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# The prognostic significance of inflammation and medullary histological type in invasive carcinoma of the breast

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ABSTRACT

The new gene expression molecular taxonomy of breast cancer places medullary carcinoma in the basal group. The basal group is considered to have a poor prognosis, but medullary carcinoma is considered to have a better prognosis than other grade 3 carcinomas. The prognostic significance of tumour associated inflammation, an important feature of medullary carcinomas, remains controversial. The aim of this study was to assess the prognostic importance of medullary histological type and inflammation in breast cancer. One thousand five hundred and ninety-seven patients who received no systemic adjuvant treatment and who had a median follow up of 9.5 years were studied. Results: Prominent inflammation was associated with high histological grade and with better survival [relative risk (RR) 0.57, 95% confidence intervals (CI) 0.44–0.74] on multivariate analysis. Typical and atypical medullary carcinomas ($n = 132$) did not have significantly different survival and were grouped together. Medullary carcinoma did not have significantly different prognosis than grade 3 ductal carcinoma with prominent inflammation, but both had a better prognosis than grade 3 ductal carcinoma without prominent inflammation ($P < 0.0001$ and $P = 0.03$). These differences were independent of other prognostic factors. These results question the current separation of typical and atypical medullary carcinoma. Prominent inflammation is associated with a better prognosis, and may explain the better prognosis in medullary carcinoma compared with grade 3 ductal carcinoma without prominent inflammation. The good prognosis of medullary carcinoma emphasises the heterogeneity of basal-like breast carcinomas. Further studies are needed to investigate the difference in survival between medullary carcinoma and other forms of basal carcinomas and the role of inflammation in any such differences in behaviour.



## 1. Introduction

Recent gene expression and immunophenotypic studies of breast cancer have reawakened interest in basal-like breast cancers and have placed medullary carcinomas in this class.[1–5] The basal group also includes non-medullary carcinomas with some medullary histological features including a lymphoid rich stroma. The basal-like class has a poor prognosis, but medullary carcinoma has been reported to be associated with a better prognosis than other grade 3 carcinomas.[6,7] The definition of medullary carcinoma and distinction from other histological types remains controversial.[8–10]

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Recently, the term medullary-like carcinoma was proposed to include both typical and atypical medullary carcinoma.[11]

The prognostic significance of inflammation, a prominent feature of medullary carcinoma, is also controversial.[12,13] Some mammary carcinomas contain the appropriate cell types required for a cell mediated immune response (macrophages, T cells and dendritic cells), but there is evidence that the function of these cells is often impaired.[14–16] Inflammatory cells can also potentially stimulate tumour growth; mechanisms include the release of proteolytic enzymes and angiogenic factors.[17,18]

This study aimed to investigate the prognostic significance of routinely diagnosed medullary carcinomas and tumour associated inflammation and the relationship between these two factors in invasive carcinoma of the breast.

## 2. Materials and methods

The study included patients with primary operable invasive breast carcinoma that was clinically less than 5 cm and treated with definitive surgery at Nottingham City Hospital between 1974 and 1988. All the patients were less than 71 years of age at the time of initial surgery. No patient received adjuvant chemotherapy or hormone therapy.

Tumours were incised immediately to ensure good fixation. The Nottingham method was used for histological grading.[19] Tumour size was based on macroscopic measurement. Lymphovascular invasion was assessed as described previously.[20] Oestrogen receptor status was assessed using the dextran coated charcoal method (cut-off 10 fmol/mg) or immunohistochemistry (cut-off H score of 10).[21] During this period the standard axillary procedure was triple node biopsy (sampling of low and high axillary and internal mammary nodes). A small proportion of women had axillary clearance. Nodes from triple node samples were bisected or cut into slices and all embedded. A single slice per node was examined from axillary clearances. Assessment of axillary nodal status was based on haematoxylin and eosin sections.

Histological type was categorised as described previously,[6] except that tubular mixed carcinomas were included with the ductal carcinomas. The diagnosis of typical medullary carcinoma required the following three features to be present throughout the tumour: (1) interconnecting syncytial sheets of pleomorphic carcinoma cells, (2) moderate or marked lymphoid infiltrate in the intervening stroma, and (3) a sharply defined margin. Little fibrous stroma is usually present. Carcinomas were classified as atypical medullary if they had a lesser degree of lymphoid infiltrate, areas of infiltrative margin or dense areas of fibrosis, while having the other features of medullary carcinoma in at least 75% of the tumour. Carcinomas with medullary features in between 10 and 75% of the tumour were classified as ductal.

An overall assessment of the intensity of lympho-histiocytic inflammation was made on haematoxylin and eosin sections by one observer (CWE), and scored semi-quantitatively into four categories (absent/minimal, mild, moderate and marked), similar to the method used by Lee and colleagues to assess diffuse inflammation as illustrated previously.[13] For survival analysis, inflammation was divided into two groups (absent and mild versus moderate and marked) as suggested by previous studies.[12,13] Moderate and marked inflammation were categorised as 'prominent'.

Patients were recruited prospectively and survival data was entered regularly. Breast cancer specific survival was defined as the interval between the first operation and death from breast cancer or death with active breast cancer. Disease-free survival was calculated from the date of first operation until the first recurrence (local, regional or distant). Univariate survival analysis was performed using Kaplan–Meier curves and log rank significance testing. Multivariate analysis of breast cancer related survival and time to relapse was performed using Cox's proportional hazards method. The median follow up was 9.5 years (range 0.06 to 30.8) with 927 breast cancer related deaths and 1086 relapses. The high mortality is probably a reflection of lack of adjuvant systemic treatment, absence of strict criteria for breast conserving surgery and limited use of radiotherapy.[22]

The research for this paper was approved by the Nottingham Research Ethics Committee 2 under the title 'Development of a molecular genetic classification of breast cancer'.

## 3. Results

### 3.1. The relation of inflammation to other prognostic factors

Prominent inflammation was seen in 9% of tumours. Increasing inflammation was correlated with increasing histological grade ($r_s = 0.46$, $P < 0.0001$), weakly correlated with increasing tumour size ($r_s = 0.12$, $P < 0.0001$) and inversely correlated with patient age ($r_s = -0.12$, $P < 0.0001$) (Table 1). The intensity of inflammation was greater in medullary carcinomas (typical and atypical) than ductal, lobular, tubular/cribriform and mucinous carcinomas ($P < 0.0001$ for all analyses, Mann–Whitney U test) and more in carcinomas of ductal type compared with lobular ($P < 0.0001$), tubular/cribriform ($P = 0.005$) and mucinous carcinomas ($P < 0.0001$). Inflammation was not related to lymph node stage ($r_s = -0.002$, $P = 0.93$).

### 3.2. Prognostic significance of inflammation

On univariate analysis overall survival was better for patients with tumours with prominent inflammation in both the complete group ($\chi^2 = 8.1$, $P = 0.004$) and in the subset of grade 3 carcinomas ($\chi^2 = 20$, $P < 0.0001$); see Fig. 1. The results were very similar for relapse free survival (all patients $\chi^2 = 7.2$, $P = 0.007$; grade 3 carcinomas $\chi^2 = 15$, $P = 0.0001$). Grade 2 carcinomas (98% of which had absent or mild inflammation) had a worse overall survival than grade 3 carcinomas with prominent inflammation ($\chi^2 = 9.6$, $P = 0.002$).

On multivariate analysis overall survival in all patients was associated with inflammation (relative risk (RR) for prominent inflammation of 0.57 (95% confidence intervals (CI) 0.44–0.74)) in addition to lymph node stage, histological grade, tumour size, and vascular invasion (Table 2). Survival was not significantly associated with oestrogen receptor status or age. Histological type was not included in this analysis. The results were similar for relapse free survival (RR for prominent inflammation of 0.67 (95% CI 0.53–0.85).

**Table 1 – Relationship between inflammation and pathological features and patient age.**

| Pathological/clinical feature | Intensity of inflammation | | | | |
|---|---|---|---|---|---|
| | Absent | Mild | Moderate | Marked | |
| Histological grade | | | | | |
| 1 | 282 (98%) | 5 (2%) | 0 | 1 | $r_s = 0.46$, |
| 2 | 501 (88%) | 59 (10%) | 9 (2%) | 0 | $P < 0.0001$ |
| 3 | 371 (50%) | 228 (31%) | 114 (15%) | 24 (3%) | |
| Tumour size | | | | | |
| 1 to 10 mm | 43 (77%) | 9 (16%) | 1 (3%) | 3 (5%) | $r_s = 0.12$, |
| 11 to 20 mm | 422 (78%) | 81 (15%) | 32 (6%) | 4 (0.7%) | $P < 0.0001$ |
| 21 to 30 mm | 447 (71%) | 115 (18%) | 56 (9%) | 10 (2%) | |
| 31 to 40 mm | 157 (64%) | 57 (23%) | 25 (10%) | 6 (2%) | |
| > 40 mm | 88 (67%) | 31 (24%) | 9 (7%) | 2 (2%) | |
| Histological type[a] | | | | | |
| Ductal/NST | 515 (66%) | 211 (27%) | 54 (7%) | 2 (0.3%) | See main text for details |
| Lobular | 171 (96%) | 6 (3%) | 1 (0.6%) | 0 | |
| Medullary | 3 (2%) | 43 (32%) | 64 (48%) | 22 (16%) | |
| Tubular/cribriform | 52 (95%) | 2 (4%) | 0 | 1 (2%) | |
| Mucinous | 16 (100%) | 0 | 0 | 0 | |
| Nodal status | | | | | |
| Negative | 714 (72%) | 172 (18%) | 82 (8%) | 14 (1%) | $r_s = -0.002$, |
| 1 to 3 nodes positive | 275 (71%) | 72 (19%) | 31 (8%) | 8 (2%) | $P = 0.93$ |
| > 3 nodes positive | 164 (73%) | 48 (21%) | 8 (4%) | 4 (2%) | |
| Patient age | | | | | |
| < 36 years | 40 (49%) | 27 (33%) | 11 (13%) | 4 (5%) | $r_s = -0.12$, |
| 36 to 49 years | 343 (69%) | 92 (19%) | 50 (10%) | 10 (2%) | $P < 0.0001$ |
| 50 to 70 years | 773 (76%) | 174 (17%) | 62 (6%) | 11 (1%) | |
| All tumours | 1156 (72%) | 293 (18%) | 123 (8%) | 25 (1.6%) | |

NST = no special type; Medullary includes both typical and atypical. Percentages are rounded, so do not necessarily add up to 100.
a Mixed types and less common types not shown.

On multivariate analysis overall survival in patients with grade 3 carcinomas was associated with intensity of inflammation (RR for prominent inflammation of 0.62 (95% CI 0.47–0.82) in addition to lymph node stage, tumour size, and vascular invasion (Table 3). Histological type was not included in this analysis. The results were similar for relapse free survival (RR for prominent inflammation of 0.71 (95% CI 0.55–0.91).

### 3.3. *Medullary carcinomas*

Forty-four carcinomas were classified as typical medullary and 88 as atypical medullary. The proportion of node-positive tumours was similar in typical and atypical medullary carcinomas (37% versus 35%, $\chi^2 = 0.003$, $P = 0.96$). The median size was identical for the two subtypes (2.2 cm, Mann–Whitney U $P = 0.85$). All except two of the 132 medullary carcinomas were grade 3. Prominent inflammation was more common in typical medullary carcinomas (82% versus 57%, $\chi^2 = 7.0$, $P = 0.008$). Prominent inflammation was not seen in all typical medullary carcinomas as the inflammation was assessed throughout the tumour, whereas the inflammation in medullary carcinoma is in the stroma between the sheets of tumour cells. There were no significant differences for vascular invasion ($P = 0.35$), oestrogen receptor ($P = 0.36$) or age ($P = 0.42$) between typical and atypical medullary carcinomas. In view of the similarities between typical and atypical medullary carcinomas, the two were combined for some of the analyses below.

Compared to grade 3 invasive ductal carcinomas, medullary carcinoma (typical and atypical) showed an association with younger patient age ($\chi^2 = 11$, $P = 0.005$), absence of vascular invasion ($\chi^2 = 17$, $P < 0.001$) and negative oestrogen receptor status ($\chi^2 = 12$, $P = 0.004$). No significant differences were seen for nodal status ($\chi^2 = 2.2$, $P = 0.33$) or tumour size ($P = 0.56$, Mann–Whitney U).

### 3.4. *Histological type and outcome*

On univariate analysis typical medullary carcinomas had a slightly worse overall survival than atypical medullary carcinomas, but this difference was not significant ($\chi^2 = 1.0$, $P = 0.32$, Fig. 2a). The presence of prominent inflammation was associated with a slightly better survival in patients with medullary carcinoma, but this difference was not significant for typical medullary carcinoma ($\chi^2 = 2.1$, $P = 0.14$), atypical medullary carcinoma ($\chi^2 = 0.02$, $P = 0.89$) or the two combined ($\chi^2 = 0.2$, $P = 0.64$, Fig. 2b).

On univariate analysis medullary carcinomas (typical and atypical combined) had a better survival than invasive ductal carcinomas overall ($\chi^2 = 15$, $P = 0.0001$), invasive lobular carcinomas ($\chi^2 = 4.7$, $P = 0.03$), both grade 2 ($\chi^2 = 8.4$, $P = 0.004$) and grade 3 invasive ductal carcinomas ($\chi^2 = 21$, $P < 0.0001$), and worse survival than grade 1 carcinomas of all types ($\chi^2 = 5.0$,

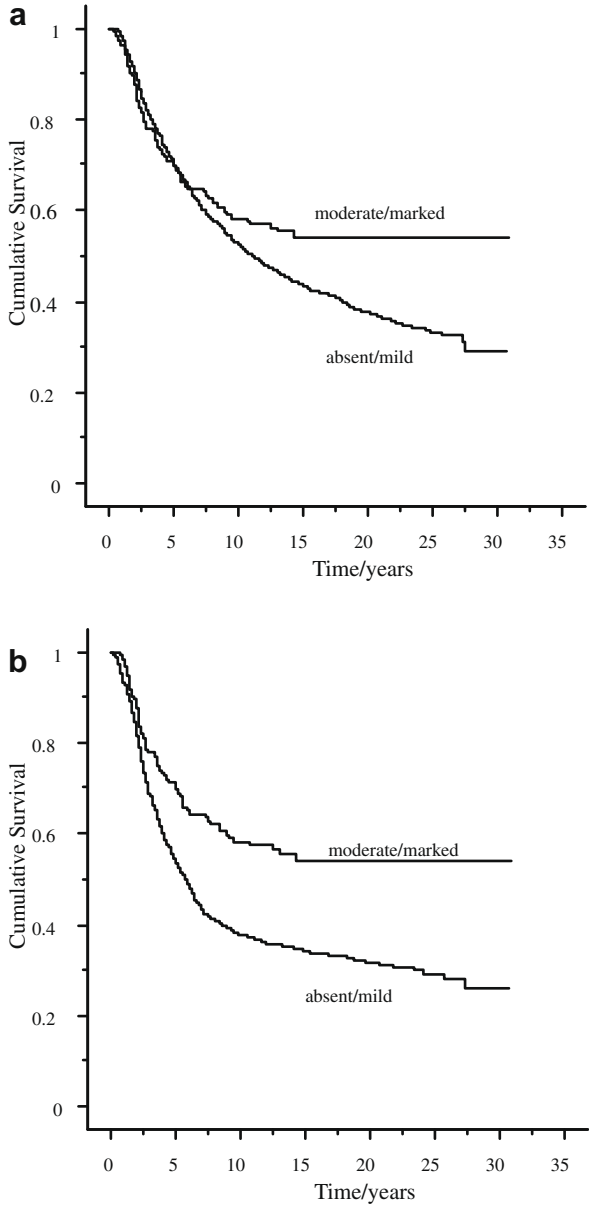


**Fig. 1 – Overall survival was better for patients with tumours with moderate or marked inflammation compared with patients with tumours with absent or mild inflammation (a) in the complete group ($\chi^2 = 8.1$, $P = 0.004$) and (b) in the subset with grade 3 carcinomas ($\chi^2 = 20$, $P < 0.0001$).**

$P = 0.03$) (see Fig. 3a). The majority of deaths from medullary carcinoma occurred within 5 years of diagnosis (68%) and 93% of deaths within 10 years. The corresponding figures were 71% and 93% for grade 3 ductal carcinomas, 41% and 68% for invasive lobular carcinomas, 46% and 79% for grade 2 invasive ductal carcinomas, and 11% and 42% for grade 1 carcinomas of all types.

### 3.5. *Histological type and inflammation*

In grade 3 carcinomas, the two most frequent histological types were ductal and medullary (the third most frequent was carcinomas of mixed type). Medullary carcinomas were almost always grade 3 (98%). The relationship of survival with histological type and inflammation was investigated (see Fig. 3b). Grade 3 ductal carcinomas with prominent inflammation had better survival than grade 3 ductal carcinomas without prominent inflammation ($\chi^2 = 4.7$, $P = 0.03$). Grade 3 medullary carcinomas (typical and atypical) had better survival than grade 3 ductal carcinomas without prominent inflammation ($\chi^2 = 24$, $P < 0.0001$). However, the difference in survival between patients with grade 3 medullary carcinomas (typical and atypical) and those with grade 3 ductal carcinomas with prominent inflammation was not statistically significant ($\chi^2 = 1.2$, $P = 0.27$), even if the analysis was restricted to tumours with moderate inflammation ($P = 0.12$). These three groups had a similar relationship to survival in multivariate analysis to that seen in univariate analysis (nodal status, vascular invasion and tumour size were all significantly related to survival).

Patients with grade 3 typical medullary or atypical medullary carcinoma had better survival than patients with grade 3 ductal carcinoma ($\chi^2 = 4.5$, $P = 0.03$ and $\chi^2 = 20$, $P < 0.0001$ respectively) and both subsets of medullary carcinoma had better survival than patients with grade 3 ductal carcinoma without prominent inflammation ($\chi^2 = 5.4$, $P = 0.02$ and $\chi^2 = 20$, $P < 0.0001$ respectively). No significant differences in survival were found between patients with grade 3 typical medullary or atypical medullary carcinoma and patients with grade 3 ductal carcinoma with prominent inflammation ($\chi^2 = 0.04$, $P = 0.85$ and $\chi^2 = 1.6$, $P = 0.20$ respectively).

## 4. Discussion

There has been a reawakening of interest in medullary carcinoma as a result of its morphological and immunophenotypical association with two of the most topical entities in breast cancer; BRCA1 associated tumours[23] and basal-like cancers.[3,4,24] BRCA1 associated tumours and the poor prognostic 'basal-like' cancer cross the spectrum of medullary carcinoma (typical and atypical) and invasive ductal carcinoma with high grade nuclei, high mitotic activity, and lymphoid rich stroma. The shared morphological features of basal-like

**Table 2 – Multivariate analysis of breast cancer related survival in all patients.**

| Factor | Relative risk | (95% confidence interval) | P value |
|---|---|---|---|
| Lymph node stage | 1.87 | (1.72 to 2.04) | <0.0001 |
| Histological grade | 1.54 | (1.40 to 1.70) | <0.0001 |
| Tumour size/cm | 1.27 | (1.16 to 1.30) | <0.0001 |
| Vascular invasion | 1.42 | (1.22 to 1.66) | <0.0001 |
| Inflammation | 0.57 | (0.44 to 0.74) | <0.0001 |

**Table 3 – Multivariate analysis of breast cancer related survival in patients with grade 3 tumours.**

| Factor | Relative risk | (95% confidence interval) | P value |
|---|---|---|---|
| Lymph node stage | 1.91 | (1.70 to 2.15) | <0.0001 |
| Tumour size/cm | 1.22 | (1.12 to 1.33) | <0.0001 |
| Vascular invasion | 1.50 | (1.21 to 1.86) | <0.0001 |
| Inflammation | 0.62 | (0.47 to 0.82) | <0.0001 |

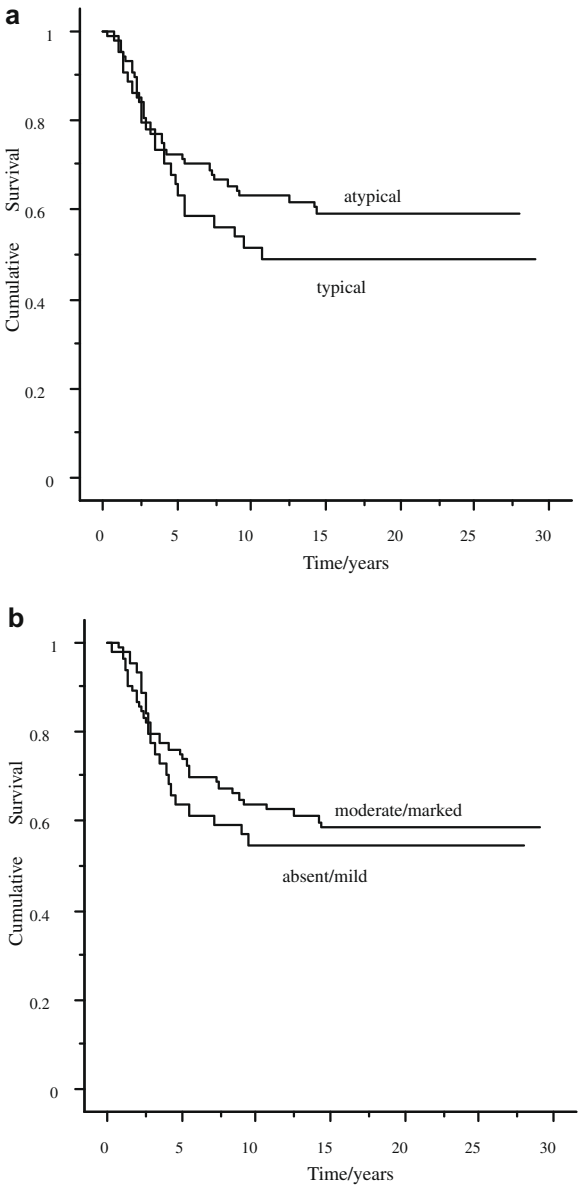


**Fig. 2 – (a) There was no significant difference in survival between patients with typical and atypical medullary carcinoma ($\chi^2$ = 1.0, $P$ = 0.32) and (b) no significant difference in survival between patients with medullary carcinoma (typical or atypical) with absent or mild inflammation compared with those with moderate or marked inflammation ($\chi^2$ = 0.2, $P$ = 0.64).**

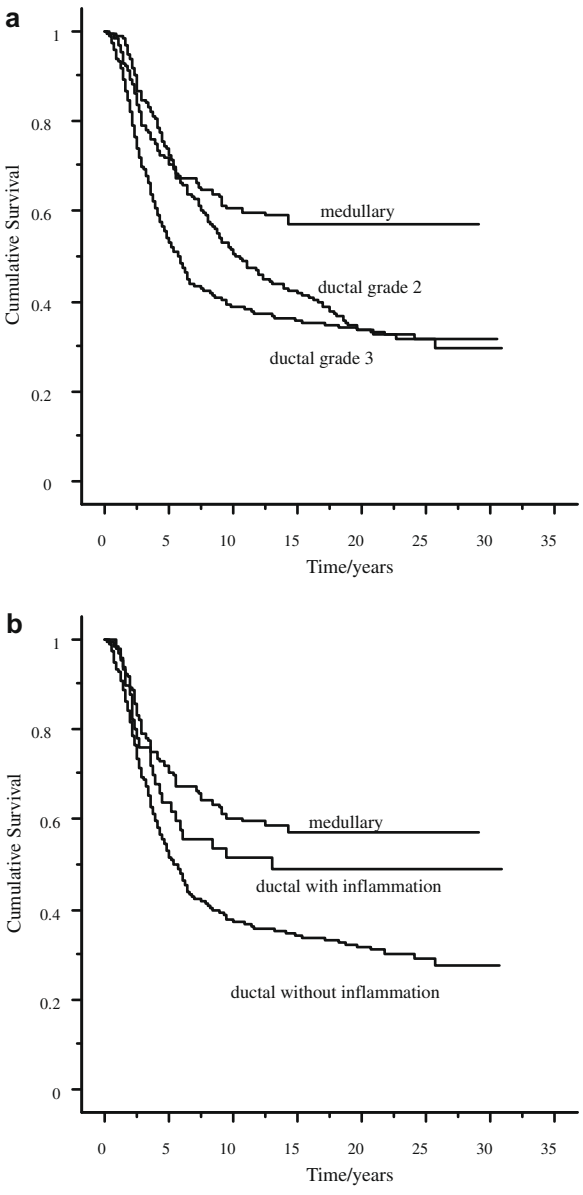


**Fig. 3 – (a) Survival was better in medullary carcinoma (typical and atypical) than in invasive ductal carcinoma grade 3 ($\chi^2$ = 21, $P$ < 0.0001), and invasive ductal carcinoma grade 2 ($\chi^2$ = 8.4, $P$ = 0.004). The survival curve for invasive lobular carcinoma was similar to that for invasive ductal carcinoma grade 2 (not shown). (b) Survival in grade 3 carcinomas was better for medullary (typical and atypical) and ductal with prominent inflammation than in ductal without prominent inflammation ($\chi^2$ = 24, $P$ < 0.0001 and $\chi^2$ = 4.7, $P$ = 0.03 respectively).**

tumours and medullary carcinoma have led some to speculate that definitions for medullary carcinoma are of limited

value. However, recent studies have reported that basal-like class of breast cancer is a heterogeneous group of tumours, which encompasses both poor and good prognostic subgroups (reviewed in 5). In addition, the role of inflammation in breast cancer remains controversial. This study investigated the prognostic significance of medullary carcinomas and tumour associated inflammation.

There are two main groups of studies investigating the prognostic significance of medullary histological type. Some start with a group of tumours originally classified as medullary and reclassify them as typical medullary, atypical medullary and non-medullary. Others, as in the present study, compare medullary carcinoma with all ductal carcinomas or grade 3 ductal carcinomas. There is also poor reproducibility in making the diagnosis.[8–10] The frequency of medullary carcinomas has decreased from about 7% in early studies to less than 1% in some recent studies.[13,25–27] Most studies only assess the relation of survival to medullary type in univariate analysis and only a few take account of nodal stage, tumour size or histological grade.

Medullary carcinoma, although not exhibiting the excellent survival characteristics of some special types of breast cancer, has consistently been observed to have a better survival than other forms of grade 3 ductal invasive carcinomas[6,7,26,28] and some studies, like the present one, find the prognosis is better than non-medullary carcinomas.[26] In addition, we found that the long term prognosis was better than invasive lobular carcinoma and grade 2 ductal carcinomas.

Small sample sizes may explain the inconsistent results on the prognostic significance of atypical medullary carcinomas. Some find that atypical medullary carcinomas have a prognosis intermediate between classical medullary and non-medullary carcinoma, whereas others find the prognosis is similar to non-medullary carcinomas.[29,30] The present study found that typical medullary carcinomas had a slightly worse survival than atypical medullary carcinomas, but this difference was not significant. The finding in the present study that atypical medullary carcinoma had a prognosis at least as good as typical medullary carcinoma questions the current strict diagnostic criteria separating these two histological types and supports the suggestion of a medullary-like type, which combines the two.

The majority of deaths due to medullary carcinoma occur within 5 years of diagnosis. The likely explanation for this is histological grade. Almost all medullary carcinomas are grade 3. The proportion of deaths within 5 and 10 years is almost identical to those for grade 3 ductal carcinomas. Also, deaths due to medullary carcinoma tend to occur earlier than with lower grade carcinomas. Despite the fact that most deaths due to medullary carcinoma are seen within 5 years, at least 5 years follow up is needed to see the separation of survival curves (see Fig. 3).

There is evidence that an effective immune response against tumours can be mounted in humans. In some tumours, such as colorectal carcinoma[31] and papillary carcinoma of the thyroid,[32] inflammation is associated with an improved prognosis. Regression is well recognised in malignant melanoma. Such patients show decreased expression of the melanoma common tumour antigen MART-1 and the presence of MART-1 specific cytotoxic T cells consistent with an antigen driven immune response.[33]

The significance of inflammation in breast cancer is controversial. The cell types required for cell mediated immune response (macrophages, T cells and dendritic cells) are present in some tumours, but spontaneous regression is extremely rare.[34] Tumour infiltrating T cells usually have little or no cytotoxic activity against autologous tumour,[14] although when such activity is present the prognosis does appear to be improved[35] Tumour infiltrating lymphocytes express low levels of Th1 cytokines consistent with the evidence of reduced cell mediated response to tumour.[15] Dendritic cells are present in small numbers in the stroma of invasive carcinomas of the breast, with little expression of dendritic cell activation markers.[36] Dendritic cells from breast cancer patients show reduced ability to stimulate control allogeneic T cells.[16] One study found the presence of higher numbers of mature dendritic cells within the tumour is associated with a better prognosis.[37] These results suggest that cell mediated immunity against the tumour is often impaired in breast cancer patients, but when these cells are functional there may be a better prognosis.

Inflammatory cells may also stimulate tumour growth. Macrophages in breast cancer secrete a variety of digestive enzymes[17], which are thought to have an important role in tumour invasion and angiogenesis. Macrophages can release growth factors such as epidermal growth factor. They can stimulate angiogenesis directly by release of angiogenic factors including vascular endothelial growth factor[38] and thymidine phosphorylase[18] and via indirect mechanisms.

The current study showed that, on multivariate analysis, prominent inflammation was associated with a better prognosis; lymph node stage, histological grade, tumour size and vascular invasion were other independent prognostic factors. This result is consistent with the majority of other similar studies of inflammation that are of adequate size and include multivariate analysis (reviewed in 13). Multivariate analysis is important because of the association of inflammation with other prognostic factors, particularly histological grade. The association of better survival with prominent inflammation suggests that the antitumour effects of inflammation, such as an immune response, predominate over the protumour effects, such as release of proteolytic enzymes and angiogenic factors.

In the present study, medullary carcinoma (typical and atypical combined) did not have a significantly different prognosis compared with grade 3 ductal carcinoma with prominent inflammation, but both had a better prognosis than grade 3 ductal carcinoma without prominent inflammation. These differences were independent of other prognostic factors and were also seen in separate analyses of typical medullary and atypical medullary carcinoma. Prominent inflammation is associated with a better prognosis, and may explain the better prognosis in medullary carcinoma compared with grade 3 ductal carcinoma without prominent inflammation. Medullary carcinomas with prominent inflammation had a slightly better prognosis than medullary carcinomas without prominent inflammation, but this difference was not significant.

The good prognosis of medullary carcinoma emphasises the heterogeneity of basal carcinomas. Further studies are needed to investigate the difference in survival between

medullary carcinoma and other basal carcinomas and the role of inflammation in any such differences. The prognostic significance of typical and atypical medullary type (and the combination of these two types) compared with other grade 3 carcinomas also merits further investigation. Such studies need adequate numbers of patients and adequate follow up of at least 5 years and ideally over 10 years (many previous studies have small numbers and short follow-up).

## Conflict of interest statement

None declared.

## REFERENCES


1. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000;**406**:747–52.
2. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA* 2001;**98**:10869–74.
3. Rakha EA, Putti TC, Abd El-Rehim DM, et al. Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. *J Pathol* 2006;**208**:495–506.
4. Jacquemier J, Padovani L, Rabayrol L, et al. Typical medullary breast carcinomas have a basal/myoepithelial phenotype. *J Pathol* 2005;**207**:260–8.
5. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. *J Clin Oncol* 2008;**26**:2568–81.
6. Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. *Histopathology* 1992;**20**:479–89.
7. Pedersen L, Zedeler K, Holck S, Schiodt T, Mouridsen HT. Medullary carcinoma of the breast. Prevalence and prognostic importance of classical risk factors in breast cancer. *Eur J Cancer* 1995;**31A**:2289–95.
8. Gaffey MJ, Mills SE, Frierson HF, et al. Medullary carcinoma of the breast: interobserver variability in histopathologic diagnosis. *Mod Pathol* 1995;**8**:31–8.
9. Anderson TJ, Sufi F, Ellis IO, Sloane JP, Moss S. Implications of pathologist concordance for breast cancer assessments in mammography screening from age 40 years. *Hum Pathol* 2002;**33**:365–71.
10. Pedersen L, Holck S, Schiodt T, Zedeler K, Mouridsen HT. Inter- and intraobserver variability in the histopathological diagnosis of medullary carcinoma of the breast, and its prognostic implications. *Breast Cancer Res Treat* 1989;**14**:91–9.
11. Third Edition of the NHS Breast Screening Programme's Guidelines for Pathology Reporting in Breast Cancer Screening and the Second Edition of The Royal College of Pathologists' Minimum Dataset for Breast Cancer Histopathology. Sheffield; 2005.
12. Rilke F, Colnaghi MI, Cascinelli N, et al. Prognostic significance of HER-2/neu expression in breast cancer and its relationship to other prognostic factors. *Int J Cancer* 1991;**49**:44–9.
13. Lee AHS, Gillett CE, Ryder K, Fentiman IS, Miles DW, Millis RR. Different patterns of inflammation and prognosis in invasive carcinoma of the breast. *Histopathology* 2006;**48**: 692–701.
14. Baxevanis CN, Dedoussis GV, Papadopoulos NG, Missitzis I, Stathopoulos GP, Papamichail M. Tumor specific cytolysis by tumor infiltrating lymphocytes in breast cancer. *Cancer* 1994;**74**:1275–82.
15. Venetsanakos E, Beckman I, Bradley J, Skinner JM. High incidence of interleukin 10 mRNA but not interleukin 2 mRNA detected in human breast tumours. *Br J Cancer* 1997;**75**:1826–30.
16. Gabrilovich DI, Corak J, Ciernik IF, Kavanaugh D, Carbone DP. Decreased antigen presentation by dendritic cells in patients with breast cancer. *Clin Cancer Res* 1997;**3**:483–90.
17. Davies B, Miles DW, Happerfield LC, et al. Activity of type IV collagenases in benign and malignant breast disease. *Br J Cancer* 1993;**67**:1126–31.
18. Nagaoka H, Iino Y, Takei H, Morishita Y. Platelet-derived endothelial cell growth factor/thymidine phosphorylase expression in macrophages correlates with tumor angiogenesis and prognosis in invasive breast cancer. *Int J Oncol* 1998;**13**:449–54.
19. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991;**19**:403–10.
20. Pinder SE, Ellis IO, Galea M, O'Rouke S, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. III. Vascular invasion: relationship with recurrence and survival in a large study with long-term follow-up. *Histopathology* 1994;**24**:41–7.
21. Bacus S, Flowers JL, Press MF, Bacus JW, McCarty KS. The evaluation of estrogen receptor in primary breast carcinoma by computer-assisted image analysis. *Am J Clin Pathol* 1988;**90**:233–9.
22. Blamey RW, Ellis IO, Pinder SE, et al. Survival of invasive breast cancer according to the Nottingham prognostic index in cases diagnosed in 1990 to 1999. *Eur J Cancer* 2007;**43**:1548–55.
23. Shousha S. Medullary carcinoma of the breast and BRCA1 mutation. *Histopathology* 2000;**37**:182–5.
24. Rodriguez-Pinilla SM, Rodriguez-Gil Y, Moreno-Bueno G, et al. Sporadic invasive breast carcinomas with medullary features display a basal-like phenotype: An immunohistochemical and gene amplification study. *Am J Surg Pathol* 2007;**31**:501–8.
25. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. *Br J Cancer* 2005;**93**:1046–52.
26. Bloom HJ, Richardson WW, Field JR. Host resistance and survival in carcinoma of breast: a study of 104 cases of medullary carcinoma in a series of 1,411 cases of breast cancer followed for 20 years. *Br Med J* 1970;**3**:181–8.
27. Anderson WF, Chu KC, Chang S, Sherman ME. Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:1128–35.
28. Gorski CM, Niepolomska W, Novak K, et al. Clinical evaluation and pathological grading in relation to other prognostic factors. In: Forrest APM, Kunkler PB, editors. *Prognostic factors in breast cancer*. Baltimore, MD: William and Wilkins; 1968.
29. Ridolfi RL, Rosen PP, Port A, Kinne D, Mike V. Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. *Cancer* 1977;**40**:1365–85.
30. Rapin V, Contesso G, Mouriesse H, et al. Medullary breast carcinoma. A reevaluation of 95 cases of breast cancer with inflammatory stroma. *Cancer* 1988;**61**:2503–10.
31. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;**313**:1960–4.
32. Fiumara A, Belfiore A, Russo G, et al. In situ evidence of neoplastic cell phagocytosis by macrophages in papillary thyroid cancer. *J Clin Endocrinol Metab* 1997;**82**:1615–20.

33. Saleh FH, Crotty KA, Hersey P, Menzies SW, Rahman W. Autonomous histopathological regression of primary tumours associated with specific immune responses to cancer antigens. *J Pathol* 2003;**200**:383–95.
34. Larsen SU, Rose C. Spontaneous remission of breast cancer. A literature review. *Ugeskr Laeger* 1999;**161**:4001–4.
35. McCoy JL, Rucker R, Petros JA. Cell-mediated immunity to tumor-associated antigens is a better predictor of survival in early stage breast cancer than stage, grade or lymph node status. *Breast Cancer Res Treat* 2000;**60**:227–34.
36. Coventry BJ, Lee P-L, Gibbs D, Hart DNJ. Dendritic cell density and activation status in human breast cancer – CD1a, CMRF-44, CMRF-56 and CD-83 expression. *Br J Cancer* 2002;**86**:546–51.
37. Iwamoto M, Shinohara H, Miyamoto A, et al. Prognostic value of tumor-infiltrating dendritic cells expressing CD83 in human breast carcinomas. *Int J Cancer* 2003;**104**:92–7.
38. Lewis JS, Landers RJ, Underwood JCE, Harris AL, Lewis CE. Expression of vascular endothelial growth factor by macrophages is up-regulated in poorly vascularized areas of breast carcinomas. *J Pathol* 2000;**192**:150–8.