Topographical and histological presentation of mammographic pathology in breast cancer

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SUMMARY Between 1979 and 1985 surgical resections from 680 cases of primary breast cancer were examined histologically. The patients were divided into four groups: (i) patients aged between 45 and 69 years who had been screened (n = 316); (ii) those younger than 45 who had not been screened (n = 55); (iii) those aged between 45 and 69 who had not been screened (n = 104); and (iv) those older than 69 who had not been screened (n = 205). The material was compared in terms of the association between in situ and invasive carcinoma. There was a low incidence of lobular carcinoma in situ (LCIS) in all groups and a high incidence of ductal carcinoma in situ (DCIS) which declined with age. Ninety nine group i patients had in situ carcinoma or early invasive carcinoma (less than 1 cm in diameter) compared with 19 of group iii cases. Screened patients had fewer multicentric cancers and a lower incidence of large invasive cancer compared with unscreened patients. Group ii patients had a higher incidence of whole quadrant in situ carcinoma, multiple cancer, and lymph node metastases. Group iv patients had a lower incidence of in situ cancer, and more low grade cancer than the other groups. Cases were divided into four types on the basis of this analysis.

The breast screening programme at the Jarvis Centre, Guildford, began in 1979. Women between the ages of 45 and 69 years were enrolled in the programme from general practices in Guildford and offered screening three times by mammography, with clinical examination at two yearly intervals, and clinical examination alone in intermediate years. The original programme was completed in 1987, but further screening of the original cohort of 25 000 women is continuing. The findings from histological examination of resections for cancer taken from screened patients between 1979 and 1985 were compared with a series of unscreened patients investigated by mammography over the same period. This paper aims to present an analysis of the histopathology of breast cancer detected by mammography in screened and unscreened women, with a classification of the results based on a combination of topography and morphology.

Material and methods

The surgical treatment of breast cancer in the Guildford breast unit has been described previously.1 Surgical specimens of breast cancer were examined from 680 consecutive patients between 1979 and 1985. The screened patients (n = 316) included those detected by screening; those presenting with symptoms of cancer between screenings, recognised as “interval” cancers; and cancers removed from patients who failed to attend for screening and who developed symptomatic tumours. The remaining patients, all unscreened, were outpatient referrals and were symptomatic. The screened patients were aged between 45–69 years, and the unscreened patients were subdivided into three age categories of less than 45 years, between 45 and 69 years, and older than 69 years. Each of these groups was compared with particular reference to the association between in situ and invasive carcinoma. Cases of recurrent carcinoma were excluded from all groups. Patients treated primarily by radiotherapy after confirmation of the diagnosis by aspiration cytology or Tru-cut biopsy were also excluded.

The surgical specimens were embedded in paraffin wax; axillary tissues were chemically cleared, and the lymph nodes were dissected.2 In the case of a full mastectomy a slice of whole breast was cut in the plane of the centre of the lesion and the nipple, and two further slices were taken at right angles to the first in line with the nipple. The slices were processed, stained with haematoxylin and eosin, and examined as single...
sections. Segmental, quadrant, and local resections were cut in the long axis of the specimen through the centre of the lesion if palpable. Alternatively, serial slices were cut when the lesion was impalpable. In all cases standard blocks were selected from the tumour and elsewhere in the breast, routinely processed, and stained. The maximum diameter of all carcinomas was measured on the stained slide but no attempt was made to subdivide tumours measuring less than 1-0 cm in diameter. The number of whole quadrants affected by carcinoma was recorded and tumours occupying more than one quadrant were subdivided as follows: (a) all tumours that invaded the central core and therefore were not amenable to local resection, (b) all tumours that affected other whole quadrants and which appeared separate and unconnected—that is, multicentric—so that even if local resection of the presenting tumour was possible, the residual breast would contain other malignant tumours. Multicentric carcinoma is defined as separate foci of either in situ or invasive carcinoma, “which are not interconnected through the duct system” (personal observation). Therefore, multiple carcinomas arising in an extensive area of in situ carcinoma were not regarded as multicentric, but documented merely as multiple cancers. The number of discrete invasive carcinomas was also noted.

The incidence of in situ carcinoma (ductal and lobular) with or without invasive cancer was noted for each group and the area of each non-invasive tumour in relation to a breast quadrant was noted. Invasive carcinomas 1-0 cm or more in diameter were typed (table 1) and graded into three categories—namely, low, average, and high grade, and the number of lymph nodes with metastases was noted. The numbers of lymph nodes with metastases in the apical, middle, or pectoral regions of the axilla were counted after examination of slides cut at two levels.

Several variables were used to test comparisons between the four groups of cases and these included an assessment of large in situ carcinomas affecting a whole quadrant, and the incidence of multicentric and multicentric carcinoma, and multiple cancers. The grades of all ductal invasive carcinomas and the incidence of lymph gland metastases in each age group were compared.

### Table 1 Tumour types in invasive carcinoma of 1-0 cm and more in maximum diameter

<table>
<thead>
<tr>
<th>Group</th>
<th>Tubular</th>
<th>Mucinous</th>
<th>Adenocystic</th>
<th>Medullary</th>
<th>Lobular</th>
<th>Intracytic</th>
<th>Carcinosarcoma</th>
<th>Ductal</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ii</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>1</td>
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<tr>
<td>iii</td>
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<td>6</td>
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<td>1</td>
<td>5</td>
<td>5</td>
<td>1</td>
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</tr>
<tr>
<td>iv</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Typing was as follows: type 1, invasive carcinoma of more than 1 cm in diameter; type 2, ductal carcinoma in situ; type 3, invasive carcinoma of less than 1 cm in diameter with or without ductal carcinoma in situ; type 4, whole quadrant ductal carcinoma in situ with or without multiple invasive carcinoma.

### Results

**LOBULAR CARCINOMA IN SITU**

LCIS was found in four of 104 (4%) cases in group ii patients; 24 of 316 (8%) cases in group i patients; six of 205 (3%) in group iii patients; and one of 55 (2%) in group iv patients. LCIS was found most often between the ages of 46–55 years (24 of 35 cases), and affected only a few lobules and was restricted to a small proportion of a breast quadrant in each case. Only two examples of quadrant sized LCIS mingled with DCIS were found and they were associated with extensive lobular invasive carcinoma. LCIS was found as a solitary lesion in one case, with ductal carcinoma in situ (DCIS) in four cases, with ductal invasive carcinoma in 13 cases, and lobular invasive carcinoma in 17 cases. LCIS has been found in half to two thirds of cases of lobular invasive carcinoma.

**DUCTAL CARCINOMA IN SITU**

DCIS occurred as an isolated malignancy (table 2) or with invasive carcinoma in all the groups, but there was a pronounced difference in staging between group i and all the other groups. Group i showed more in situ and small invasive carcinomas and fewer large tumours. All unscreened groups showed a low
incidence of in situ carcinoma and large invasive carcinoma predominated. Group iv cases had the lowest proportion of in situ carcinoma, but there were more well differentiated invasive carcinomas than in the other groups and some less common varieties not associated with DCIS.

DCIS was found in 251 of 316 (80%) breasts removed for cancer in group i cases, and in 92 of 104 (94%) in group ii cases, 149 of 205 (74%) in group iii cases, and 32 of 55 (58%) in group iv cases.

**Quadrant Sized Ductal Carcinoma In Situ**
All groups showed a proportion of large (extensive) DCIS and these were compared to give an estimate of variations in the extent of breast affected by DCIS in each of the groups. For this investigation cases in which DCIS had spread throughout a duct system that could be traced through the entire radius of one whole quadrant were compared, even though there was variation in the degree of disease in small tributaries. This degree of quadrant disease could only be judged effectively in mastectomy specimens. The results (table 3) show that the numbers of whole quadrant DCIS were similar in all groups, with the exception of group ii where there were twice as many. Whole quadrant DCIS occurred throughout the age range (table 4) with a peak in the fourth and fifth decades. The youngest patient was 29 years and the oldest 81 years. Sixty seven of 82 cases of large DCIS showed invasive carcinomas.

**Multiple Quadrant Disease**
Single or multiple quadrant disease of the breast was assessed in all women who had a mastectomy for invasive carcinoma 1.0 cm or more in maximum diameter, as most small tumours were treated by limited resection. The results were similar for all groups. Multiquadrant disease was found in 30 of 138 (22%) mastectomy specimens in group i cases and in 16 of 55 (29%) group ii cases, 37 of 122 (31%) group iii cases, and seven of 28 (25%) group iv cases. Malignant tumours affecting more than one whole quadrant (multiquadrant) are generally not amenable to local resection.

**Table 6 Grading**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Carcinoma 1.0–2.0 cm</th>
<th>Carcinoma &gt; 2.0 cm</th>
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</thead>
<tbody>
<tr>
<td>Group i</td>
<td>Low 37 (30%)</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>Average 70 (56%)</td>
<td>28 (44%)</td>
<td></td>
</tr>
<tr>
<td>High 17 (14%)</td>
<td>21 (33%)</td>
<td></td>
</tr>
<tr>
<td>Total 124</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Group ii</td>
<td>Low 6 (17%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Average 19 (54%)</td>
<td>28 (67%)</td>
<td></td>
</tr>
<tr>
<td>High 10 (29%)</td>
<td>11 (26%)</td>
<td></td>
</tr>
<tr>
<td>Total 35</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Group iii</td>
<td>Low 20 (25%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Average 52 (64%)</td>
<td>53 (58%)</td>
<td></td>
</tr>
<tr>
<td>High 9 (11%)</td>
<td>28 (31%)</td>
<td></td>
</tr>
<tr>
<td>Total 81</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Group iv</td>
<td>Low 17 (39%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Average 10 (56%)</td>
<td>13 (60%)</td>
<td></td>
</tr>
<tr>
<td>High 1 (5%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Total 18</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>
Table 7  Management of breast cancer in 680 cases (1979–85 inclusive)

<table>
<thead>
<tr>
<th>Patey mastectomy</th>
<th>Segmental resection and node clearance</th>
<th>Simple mastectomy</th>
<th>Local excision</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened patients with histology including interval cases (45–69 years) (i)</td>
<td>145 (46%)</td>
<td>7 (2%)</td>
<td>21 (7%)</td>
<td>143 (45%)</td>
</tr>
<tr>
<td>Unscreened patients &lt; 45 years (ii)</td>
<td>66 (63%)</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
<td>34 (33%)</td>
</tr>
<tr>
<td>Unscreened patients 45–69 years (iii)</td>
<td>122 (59%)</td>
<td>5 (2%)</td>
<td>17 (8%)</td>
<td>61 (30%)</td>
</tr>
<tr>
<td>Unscreened patients &gt; 69 years (iv)</td>
<td>24 (44%)</td>
<td>0</td>
<td>4 (7%)</td>
<td>27 (49%)</td>
</tr>
</tbody>
</table>

MULTICENTRIC CARCINOMA

Multicentric carcinoma was found in only 11 of 166 (7%) mastectomy specimens in group i cases, but there were 13 in 69 (19%) in group ii cases, and 20 in 139 (15%) in group iii cases. No multicentric carcinomas were found in group iv cases but numbers were small.

Twenty one of the 44 cases of multicentric carcinoma in the whole series were found in breasts that also had whole quadrant sized in situ carcinoma (n = 82).

Multiple invasive carcinomas were found in nine of 166 (5%) mastectomy specimens from group i cases, and there were 14 of 69 (20%) in women in group ii, 14 of 139 (10%) in group iii, and one of 28 (4%) in group iv cases.

LYMPH NODE METASTASES AND GRADING

No lymph node metastases were found in 20 cases of Patey mastectomy for invasive carcinoma of less than 1 cm in maximum diameter, but the incidence for invasive carcinomas of 1 cm and larger was high in all groups (table 5), and particularly so in group ii. There was no correlation between tumour size and grade in group ii cases, but there was in groups i, iii, and iv (table 6) where large invasive cancers were of higher grade than small cancers. The increased incidence of high grade tumours among small carcinomas is reflected in the higher incidence of axillary lymph gland metastases in women younger than 45 years, compared with other age groups. There were less high grade tumours in those 69 years and older.

Fig 1  Type I breast cancer (55 year old woman). Invasive duct carcinoma of breast with satellite tumour. (Haematoxylin and eosin.)
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Fig 2  Type 2 breast cancer (46 year old woman). Focal in situ ductal carcinoma of breast. (Haematoxylin and eosin.)

Discussion

A comparative study of breast cancer in a sequential series of patients relies on the absence of selectivity of data for the validity of the conclusions. Specialist centres may introduce an element of selectivity if patients are referred from outside the clinical area or district, but the patterns of referral in each of the groups showed no clear evidence of this. The comparison between the screened group as a control and the unscreened group of similar age did not indicate any pronounced differences and those differences which were found were logically explicable.

The analysis of the results showed that the predominant presenting malignant tumour of the female breast was ductal carcinoma, both in situ and invasive. Lobular carcinoma in situ had a relatively minor role and did not present as the primary abnormality in symptomatic or screened women investigated by mammography. Breast cancer detected by mammography can be subdivided into four main types on the basis of the histological and topographical analysis of the series. The first type includes all invasive cancers 1 cm and over in maximum diameter (tables 1 and 2) and represents most cases (fig 1). The second type consists of ductal in situ cancer alone (fig 2). The third type includes all small invasive cancers of less than 1-0 cm in maximum diameter that are either visible alone in the mammogram or associated with microcalcification and ductal in situ carcinoma (figs 3 and 4). The fourth type is formed by giant in situ ductal cancers of whole quadrant size (figs 5 and 6) which usually have extensive microcalcification and are often the site of origin of one or more discrete invasive cancers (fig 7).

**TYPE 1**
The incidence of invasive cancer of 1 cm or more in

Fig 3  Type 3 breast cancer (52 year old woman). Small invasive duct carcinoma of breast arising from in situ ductal carcinoma. (Haematoxylin and eosin.)

Fig 4  Type 3 breast cancer (48 year old woman). Small invasive duct carcinoma of breast in patient with multicentric tumours. (Haematoxylin and eosin.)
maximum diameter in this series varied between 69% of all cancers in group 1 cases to between 81 and 94% in all the other groups. The cancers were mainly ductal with a small percentage of other types (table 1). The difference between the screened and unscreened groups was due to the reduction of large cancers (more than 2 cm in maximum diameter). Axillary lymph node metastases varied between 22 and 57%, depending on tumour size and age group (table 5). Carcinomas of more than 2 cm maximum diameter had a higher incidence of axillary metastases than smaller cancers and women younger than 45 years had the highest incidence of lymphatic metastases in the 1–2 cm tumour range. A substantial proportion of this group had a metastatic spread beyond the breast at the time of diagnosis and had no prospect of curative surgery. These findings confirm the view of many surgeons that the aim of surgery should be the control of local disease. Between a fifth and a third of all mastectomy specimens, however, showed multiple quadrant neoplasia so that the prospects of control by local excision alone were probably doubtful.

**Type 2**

Ductal carcinoma in situ is usually small and focal but can be detected by mammography in an unknown percentage of cases because degeneration of ductal malignant cells produces the characteristic branching microcalcification visible in the radiograph, and which can be distinguished from focal calcification seen in proliferative dysplasia and duct cysts. Group 1 cases showed between three and four times the amount of ductal cancer in situ found in the unscreened groups, except in women younger than 45 years where the incidence was higher (table 2).

**Type 3**

This group of early invasive cancers was detected by mammography in 17% of screened patients compared with an average of 5% in unscreened patients. About 80% of small invasive cancers (less than 1 cm) showed foci of in situ carcinoma. The small number of tiny invasive cancers detected in symptomatic unscreened women were usually found by mammography but several were palpable. Axillary lymph nodes were removed from only a small number of patients but the absence of metastases in all suggests a good prognosis if local disease is cured by surgery.

**Type 4**

Whole quadrant carcinoma in situ with or without invasive cancer was found in all age groups but was
twice as common in women younger than 45 years; the incidence was constant for all other groups whether screened or unscreened (table 3). This is consistent with type 2 cases in which a high incidence of carcinoma in situ was found in the younger women. Most large carcinomas in situ showed one or more invasive cancers, but in the screened group about a third of cases were free of invasive cancer compared with an eighth in unscreened groups. Most of these large lesions were detected in the early rounds of the screened group. Type 4 cases also showed unconnected foci of cancer elsewhere in the breast and accounted for half the cases of multicentric carcinoma. The incidence of type 4 breast cancer declines in later decades but persists into old age.

**Natural History of Breast Cancer**
This investigation has thrown some light on the natural history of breast cancer. An hypothesis can be made about the pattern of ductal carcinoma in situ throughout life by using the data on whole quadrant lesions as a mirror to reflect the changing incidence with age. Ductal carcinoma in situ is more prominent during the reproductive period of life and apparently reaches a peak incidence in unscreened women aged between 45 and 50 years—five years earlier in screened women. The incidence declines to a steady state at 65 years which persists into old age. Large in situ carcinomas are related to the high incidence of multiple invasive carcinomas and multicentric tumours found in women younger than 45 years, and there are more high grade invasive cancers and lymph gland metastases than in older women. Unfortunately, clinical information about the prognosis of breast cancer in women in the reproductive period of life is difficult to assess due to the lack of precise pathological staging, and variable results have been published. Thus in clinical studies of women 35 years and younger some consider the prognosis to be unfavourable, about the same, or more favourable. Breast cancer still remains a lethal disease in the elderly, mainly because possible clinical advantages (more low grade invasive cancers) are outweighed by the effect of pathological staging.

**Influence of Breast Screening on the Laboratory**
The screening programme staging analysis as presen-
Thereafter, the number of cancers with a prescreening level, 9% in unscreened patients of equivalent age. During the first two years of the programme the number of large cancers was increased by the discovery of tumours that were about to become symptomatic. Thereafter, the number of cancers fell back to the prescreening level, and the large tumours diminished but did not disappear due to the appearance of "interval" cancers that escaped detection in the screening rounds. The screening programme also included cancers that appeared in women who failed or refused to attend, and most of these were large tumours. It is obvious that poor compliance in a screening population will greatly impair results and may lead to no overall benefit. The Guildford screening programme has a compliance of 69% compared with more than 80% in Sweden.

Histologists should therefore plan their strategy before the programmes begin. Experience at this Centre suggests that surgeons will want to confirm the diagnosis before operation so that fine needle aspiration cytology and, in some cases, Tru-cut biopsy, can replace frozen section diagnosis at operation, leaving the latter to be used only as a last resort. In any event frozen section diagnosis should be avoided in doubtful or minimal lesions. Preoperative diagnosis takes the pressure off the histologist who should be encouraged to produce a full and unhurried pathology report.

As the programme proceeds many excision biopsies can be done with the aid of preoperative localisation by the radiologist with dyes or hooks (table 7). These biopsy specimens should be checked by specimen radiography and then sent to the laboratory with the mammograms and clinical notes. The biopsies should be cut into slices before or during fixation and each slice blocked in toto, because abnormalities may not be visible macroscopically and clearance margins have to be assessed. This technique requires the availability of a sledge microtome with a stage able to accommodate paraffin blocks of about 5 cm². Larger blocks and hemisections of the breast may be cut by histologists with a special interest, multicentric breast disease, for example, but appropriate microtomes will be required for this. Large tissue blocks can be processed by standard machines. Benign biopsy specimens require the same technique to exclude malignancy and to relate the lesion to the mammogram. The number of benign biopsy specimens will outnumber the malignant lesions in the early years before falling to parity i.e. the later screening rounds as experience is gained.

Consistent measurement of invasive cancers is necessary for staging purposes, and the maximum
measurement of diameter is usually obtained from the stained slide because macroscopic measurements on fresh or fixed tissue may minimise the lesion. The number of axillary dissections in this series diminished with the fall in tumour size, but these can be burdensome to the pathologist. In this study all axillary lymph glands were dissected after fat solution and clearance of tissues which resulted in a much higher yield and a great saving in time.2

Finally, thought should be given to the documentation of results because histopathology should give an early indication of the performance of the screening programme, which is not surprising as it forms the diagnostic base on which all else depends.

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References


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