Deprivation and Pathological Prognostic Indicators in Operable Breast Cancer.

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List of publications

Abstracts:

Incidence of Lymph Node Metastases in Infiltrating Breast Cancers of less than 10mm.

CM Sharp, C Wilson, JC Doughty, WD George.

European Journal of Cancer, vol 37, supp 5: 34. Sep 2001.

Incidence of Lymph Node Metastases in Infiltrating Breast Cancers of less than 10mm.

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Incidence of Lymph Node Metastases in Infiltrating Breast Cancers of 10mm or Less.

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List of abbreviations

ANC	Axillary node clearance
ANS	Axillary node sample
ALND	Axillary lymph node dissection
ER	Oestrogen receptors
HRT	Hormone replacement therapy
LVI	Lymphovascular invasion
NPI	Nottingham prognostic index
OCP	Oral contraceptive pill
SLNB	Sentinel lymph node biopsy
-ve	Negative
+ve	Positive

Thesis Summary

Introduction

The aim of this study was to assess the effect of deprivation on pathological prognostic indicators in breast cancer and to find a population of patients with breast cancer who are unlikely to have axillary metastases and therefore be spared axillary clearance.

It is well recognised that patients from deprived areas with breast cancer have a poorer outcome. The reasons for this are unclear. Some studies have found that patients from deprived areas are more likely to have oestrogen receptor negative tumours, which have a poorer prognosis. Others have found no relation between deprivation and pathological prognostic factors and suggest poorer outcome may be due to late presentation or impaired host responses secondary to, for example, co-morbidity, genetic, diet or environmental factors.

Axillary clearance provides information for staging and prognosis and may also provide local control and even cure as well as aiding in the decision to give adjuvant treatment. However it carries with it significant morbidity such as lymphoedema, paraesthesia and reduced shoulder mobility.

Recently much work has been done into the role of sentinel node biopsy as a means of assessing the axilla for metastases, but there is still a false negative result of up to 10% with this procedure. It has been found that sentinel node biopsy is more effective in patients at low risk of axillary spread.

It has been found in other studies that the incidence of nodal metastases in patients with tumours of 10mm or less is low. Some studies of tumours of 5mm or less have had an incidence of axillary metastases of 0% and some suggest abandoning axillary clearance in these patients. Other studies of tumours up to 10mm have had as many as 27% with positive nodes.

We wanted to find out whether deprivation in the Glasgow area had any effect on tumour pathology and lymph node spread which may account for poorer outcome. We also wanted to find out which patients with small tumours were least likely to have nodal spread, and therefore be spared axillary clearance or provide a target population for assessment with sentinel node biopsy.

Method

The data was collected prospectively from five hospitals in the Glasgow area and included all patients who had breast cancers operated on between

October 1995 and March 2001. They included both screen detected and symptomatic patients.

Patients were separated into three groups – affluent, intermediate and deprived according to the Carstairs index of deprivation at the time of diagnosis. This is a deprivation score based on area of residence using census data. The influence of deprivation on the pathological size of the tumour, histological grade, ER status, axillary node status and Nottingham prognostic index (NPI) were examined. Deprivation data was available for 3251 patients.

In total there were 666 patients who had tumours of 10mm or less. We excluded those who had less than 4 axillary nodes excised when looking at the incidence of nodal metastases in these patients as it was assumed that some might not have had their axillae accurately assessed. Those with ungraded tumours were also excluded leaving 613 patients in this part of the study. 64% were screen detected. Deprivation scores were available for 608 of these patients.

The pathological variables we examined were size, which we split into those of 5mm or less (T1a) and those of 6-10mm (T1b). We also looked at size as a continuous variable. The other variables were histological grade, the presence of lymphovascular invasion and ER status.

Results

When we looked at the effect of deprivation on ER status, size, grade, node status and NPI the deprived patients were significantly more likely to have high grade tumours. 27% of affluent, 30% intermediate and 35% deprived had grade 3 tumours ($p<0.02$). We also found that they had significantly larger tumours at operation. 33.3% of affluent, 35.6% of intermediate and 43.4% of deprived had tumours of greater than 20mm ($p<0.001$). Significantly fewer of them had been screen detected ($p<0.01$) suggesting they are presenting later. Deprived patients were more likely to be ER negative ($p=0.016$). There was no significant relationship between deprivation and nodal status. Because deprived patients had larger tumours at operation and had a higher incidence of grade 3 tumours, they were significantly more at risk according to NPI ($p<0.01$).

Similar results were seen when we assessed those with tumours of 10mm or less. We found that patients in the deprived group were significantly more likely to have higher grade tumours with 11.1% of affluent, 15.4% of intermediate and 21.7% of deprived patients having grade 3 tumours ($p= 0.032$). There was a trend for the more deprived patients to have a higher incidence of ER negative tumours with 11.3%, 17.9% and 19.3% of patients In the affluent, intermediate and deprived groups having a negative ER status respectively. This however was not significant ($p= 0.073$). More patients in the deprived group had lymphovascular invasion present, 13.9% compared to 10.6% and 10.4% in the intermediate and affluent groups ($p= 0.3$), however

there was no relationship between nodal spread and deprivation (p=0.9), nor was there any significant difference in NPI between the groups (p=0.3) although a higher proportion of the affluent group had a low risk NPI. Presumably because size is essentially being removed from the equation.

Of all the patients with tumours of 10mm or less 18.1% of had positive nodes. There was a trend for the larger size tumour to have an increased incidence of positive nodes with 13.4% of T1a and 19.2% of T1b tumours being node positive. This difference was not significant, but when we looked at size as a continuous variable it was a significant indicator of nodal spread ($p<0.001$). A higher grade was also a significant indicator of nodal spread with 11.4% of grade 1, 21% of grade 2 and 31.3% of grade 3 tumours having positive nodes ($p<0.001$).

We looked at the influence of size within each grade and the trend for the larger size tumours to be more likely to have nodal disease is still there in grades 1 and 2, but not for the grade 3 tumours. This finding is most likely because of the smaller numbers in this group with only 16.2% of patients having grade 3 tumours.

The most important indicator of lymph node spread was the presence of lymphovascular invasion. 13.4% of patients with tumours without lymphovascular invasion were node positive compared to 54.3% of those where lymphovascular invasion was present ($p<0.001$).

The influence of lymphovascular invasion within each grade was also examined. There was a higher incidence of positive nodes when lymphovascular invasion was present and this was true for each grade. It was not significant in the grade 3 group and again this is most likely because of the smaller number in this group.

When we looked at ER status, as a single variable, those with ER negative tumours were significantly more likely to have axillary metastases than those with ER positive tumours ($p=0.038$). 16.5% of ER positive tumours and 25.7% of ER negative tumours were node positive. However, when we corrected the ER status for the other three variables with a multivariate analysis it was no longer a significant factor.

According to our multivariate analysis the most important predicting indicator was lymphovascular invasion with a greater than five fold increase in risk of having positive nodes if lymphovascular invasion was present. Next was grade with a relative risk of 1.51 for each step up in grade and then size with a relative risk of 1.15 for each millimetre increase in size.

Low risk tumours are those of grade 1 without lymphovascular invasion. In total 9.5% of them were node positive. Of those 5mm or less 5.7% were node positive. None of the patients with grade 1 tumours of less than 5mm without lymphovascular invasion had axillary metastases, although the number in this group was very small.

Conclusion

It would appear that deprived patients are presenting later with bigger, more aggressive tumours and fewer have small low risk cancers. This is possibly partly due to co morbidity, genetic or environmental factors, but also may be due to fewer deprived patients attending for screening.

Although deprived patients with small cancers of 10mm or less were significantly more likely to have high grade tumours and had a higher incidence of LVI there was no relationship between nodal spread and deprivation. This was true even when looking at tumours of all sizes.

We have found that axillary metastases from tumours of 10mm or less do occur. In this study even in those with tumours of 5mm or less the incidence of positive nodes was 13.4%. We therefore cannot routinely omit axillary clearance in these patients.

Risk of lymph node spread is multifactorial. Patients with small, low grade tumours without lymphovascular invasion are least likely to have nodal disease. It may be that these patients can provide a target population for assessment with sentinel node biopsy prior to the decision to omit clearance.

Introduction

CHAPTER 1

Introduction

1.1

Breast cancer incidence and mortality

Breast cancer is the commonest type of cancer in women. 18% of all cancers in females are breast malignancies. There are around one million new cases per year worldwide. [1]

In Britain it will affect around 1 in 10 women during their lifetime. Around half of these will be in women over the age of 65 with the majority occurring in women over 55. It was the most common cause of cancer death in women until 1999, but since then there have been more deaths from lung cancer. It is the commonest cause of death in women in the 35-54 year old age group accounting for 17% of all deaths.[2]

The incidence of breast cancer has continued to gradually increase over the past few decades. There was a steep increase in incidence in the 1980s which coincided with the introduction of the breast screening programme and reflected an increase in detection rates. (figure 1). Screening aside, the incidence of breast cancer in many parts of the world continues to rise especially in low risk areas.[3] Despite this, however, standardised mortality

rates are levelling off.[4, 5, 6] In 2003 there were 12,614 female breast cancer deaths in the UK compared to 15,625 in 1989.[2]

This may be due to a combination of things such as improved treatments and the increased detection of smaller, better prognosis tumours from screening. Survival increase may also be explained partly by improvements in organisation and delivery of care. [7]

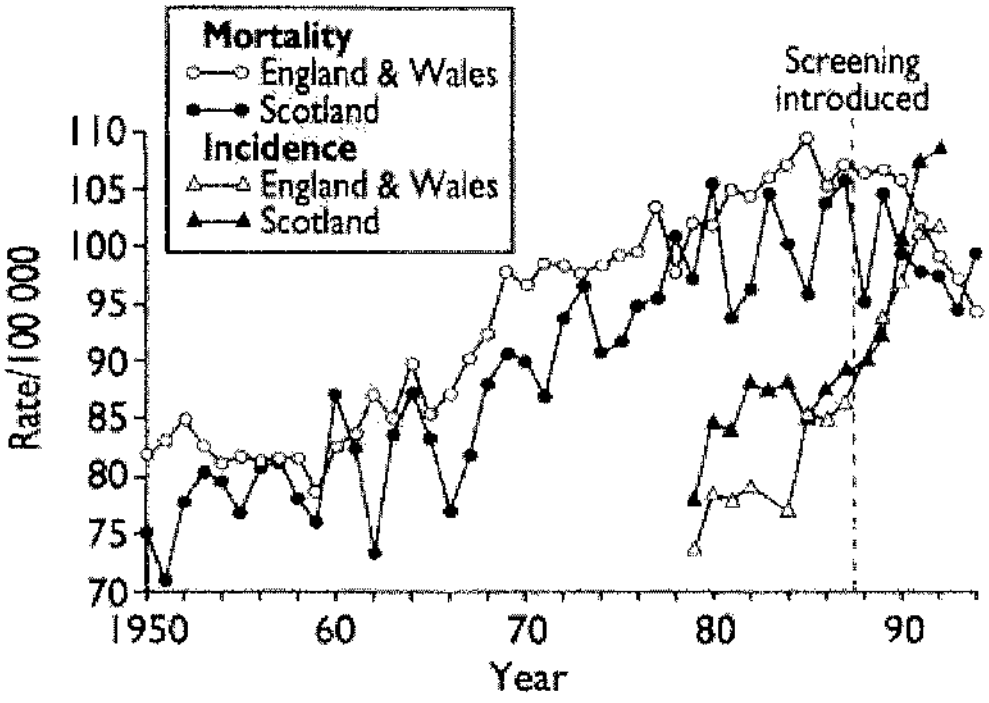


Figure 1. Incidence and mortality from breast cancer in Britain at introduction of screening. Graph from Brewster D, et al. BMJ 312: 7031. March 1996.

The reason for the continuing gradual increase in breast cancer is unknown and probably multifactorial as is the aetiology.

1.2

Breast Screening

Breast screening was introduced in Scotland in 1988 although was not universally available until 1991 and the first round was completed in 1994.

There are five criteria for any screening programme:

- The condition must be common with serious consequences.
- An identifiable precursor or marker is required and the screening test has to have a high sensitivity and specificity for detecting these.
- Treatment of screen detected disease has a better outcome than that of the symptomatic disease.
- The screening test has to be acceptable to the patient.
- The screening programme has to be cost effective.

The first point, the condition must be common with serious consequences, is undoubtedly true for breast cancer. As mentioned above it is the most common cancer in women and is responsible for around 12,600 deaths each year in Britain.

The precursor, or marker, in breast cancer is the pre-malignant (carcinoma in situ), early invasive and/ or impalpable breast lesion as seen on mammography. Mammography is the only tool that has been shown to be effective for early detection of these lesions. It has a sensitivity of around 90% (That is, the ability to detect disease in those who have it.) and a specificity of around 95-99% (The ability to exclude disease in those who do

not have it.).[8] There is no evidence that clinical examination, ultrasonography or teaching self examination is effective. [9]

Thirdly, the treatment of the screen detected disease should have a better outcome than that of the symptomatic disease. Initially critics of breast screening felt that it would not reduce mortality. They thought it would simply introduce lead time bias (detecting cancers earlier would give the impression that women were surviving longer), length time bias (detecting slower growing, less lethal cancers) and selection bias (women opting to have screening may mainly be from one particular background, for example higher socioeconomic status).

As already discussed and as can be seen in figure 1, despite a gradual increase in incidence of breast cancer (some of which is due to the introduction of screening itself), mortality from the disease is falling. This, in part, is due to breast screening. Several randomised controlled trials have shown that mammographic screening can significantly reduce mortality from breast cancer in those who attend. Nystrom et al showed in their overview of Swedish screening trials a 29% reduction in mortality in women screened between the ages of 50 and 69 years of age over a 12 year follow up period. There was no significant reduction in mortality in women of 40-49 years (mammography is less sensitive in younger age groups) and only marginal improvement in those 70-74 years.[10] Similar results were seen in a meta-analysis by Kertilowski et al.[11] An early trial from Edinburgh showed only a

20% reduction in mortality in women over 50 years of age who were screened over a 7 year follow up period. Compliance with screening in this study, however, was poorer.[12] Over 70% of the target population need to attend if mortality is to be reduced significantly.[9] In Scotland the uptake for screening is around 74% although this varies slightly between health board areas and areas of different socioeconomic class.[13]

Another positive outcome measure with mammographic screening includes a better cosmetic outcome with more breast conservation owing to the finding of smaller tumours at mammography.

The screening test obviously has to be acceptable to the target population or compliance with the screening will decline and the effect on mortality reduced. Mammography is non invasive although can be uncomfortable for the patient. The lifetime risk of breast cancer arising from the radiation exposure during the screening is minimal.[14] In general mammography is seen as an acceptable screening method.

Lastly, the screening programme has to be cost effective. Up until recently, in Britain, screening was offered to women between the ages of 50 and 64 and was available on a voluntary basis in older age groups. Now women of up to 70 years of age are being invited routinely although this is not occurring everywhere in Scotland as yet. That is, it is offered to women in whom it has been shown to be of most benefit with regards to reducing mortality.

Screening in the younger age groups would increase the cost per life year saved. There is no benefit with regards to reduction of mortality by screening any more frequently than every 2 years (in an attempt to reduce numbers of interval cancers) and this would therefore only reduce cost effectiveness.[11] In Britain, women are invited routinely every 3 years. At each screen an oblique and craniocaudal view mammogram is taken. This increases the detection rate of cancers by 24% and this increased detection rate, in turn, does not make it any less cost effective.[15] As mentioned above, compliance with screening has to be over 70% to have a significant effect on mortality and to maintain cost effectiveness. Thus it is important that the screening programme is adequately organised with accurate patient lists and the target population are educated as to the benefits of screening and are encouraged to attend.

Also of consideration is the cost to the patient such as anxiety regarding the result, risk of false positives and harm of negative biopsies and inconvenience. With adequate patient education and a well trained multidisciplinary assessment team the overall experience causes little more anxiety in screened women than in controls.[9]

1.3

Risk factors

There does not appear to be one single cause of breast cancer. Its aetiology is multifactorial, however there are some established and probable risk factors for the disease.

1.3.1 Age

The risk of breast cancer increases with age. The incidence roughly doubles every 10 years. After the menopause the risk continues to increase, but at a slower rate.

1.3.2 Reproductive history

Early onset of menstruation and late menopause are both risk factors. It has been found that women who have the menopause before the age of 45 have half the relative risk of breast cancer than women who are over 55.[16] Factors which delay onset of menstruation such as physical activity or produce an early menopause such as oophorectomy have a protective effect.

Age at birth of the first child also effects breast cancer risk. Women who are nulliparous or have their first child when they are over the age of 30 have a risk double that of those who have a child when they are under the age of 18.[17] There is no evidence to suggest that abortion either spontaneous or induced increases breast cancer risk.[18] From the above it can be seen that

greatest risk lies with those who have a longer period of uninterrupted menstrual cycles.

1.3.3 Exogenous hormones

Increased exposure to oestrogens is thought to increase breast cancer risk. Many studies have shown that women taking or who have taken the oral contraceptive pill (OCP) are at an increased risk of breast cancer. In general though, the increase in risk compared to those who have never taken the oral contraceptive pill is slight and reverts to normal female population risk 10 years after stopping. It would also appear that breast cancers diagnosed in women who have taken the OCP are less advanced than in those who have not. It is not known whether this is due to earlier detection, the effects of the hormone, or both. [19]

Similarly, hormone replacement therapy (HRT) increases risk and has an effect akin to that of delaying menopause one year for each year of therapy i.e. the risk increases with duration of use. The risk remains elevated for 5 years after stopping. There does not appear to be any higher mortality from breast cancer in women on HRT. As with OCP use cancers detected in women who have at some stage taken HRT seem to be less advanced. [20]

1.3.4 Country of residence

There is a wide variation in incidence and mortality rates between different countries. The incidence can vary five fold between country around the world.

In general more westernised countries have a higher incidence and mortality. In some Western countries there is greater than 100 cases per 100000 women compared to 10-15 cases per 100000 women in Asia.[21] As previously mentioned the rates of breast cancer are increasing and the rate of increase is highest in those low risk countries. This may be due in part to marked lifestyle changes in these countries over the last 50 years.

Japan has one of the lowest incidences of breast cancer in the world at around 20 cases per 100000 population. Low rates here can be partly, but not completely explained by the later age of menarche and lower rate of nulliparity in Japanese women.[21] It has been shown that when women from low risk countries emigrate to a high risk country their offspring will, within one or two generations take on the rate of their new country of residence. This suggests that environmental factors have more influence on risk than genetic factors. [22]

1.3.5 Diet

Some studies have suggested that high dietary fat intake may increase risk of breast cancer and that this may to some extent explain some of the geographical differences as more Westernised countries tend to have more fat in their diets. There is also some evidence that there is a protective role of monounsaturated fats and omega 3 fatty acids. For the most part, the relationship between diet and risk is largely inconclusive. [23]

1.3.6 Weight and weight gain

Several studies have shown that a high body mass index (BMI) in pre menopausal years has a protective effect on breast cancer risk, but post menopausally a high BMI or weight gain can increase risk. [24, 25] One hypothesis on why this may be so is again related to oestrogen exposure in that premenopausal obesity can be related to anovulation and the fact that oestrogens are produced in adipose tissue in postmenopausal women.[25] It has never been shown, however, that obese females have higher levels of oestrogen.

1.3.7 Smoking and Alcohol

There is no relationship between smoking and breast cancer.[26]

Alcohol intake has been shown to have a positive effect on breast cancer risk in developed countries. Even after correction for confounding variables such as smoking, race, education, family history, use of exogenous hormones and reproductive history it may be attributable for about 4% of breast cancers. For women who regularly drink alcohol the lifetime risk of breast cancer is estimated to increase by approximately 0.7 per 100 women for each unit of alcohol consumed per day. [26]

1.3.8 Genetic Influence

Family history is the most widely recognised risk factor for breast cancer. Evidence for genetic predisposition was derived originally from the observation of cancer clustering in families. This may be attributed to both shared genes and to shared environments and lifestyles. Most studies show around a 2 fold risk for women who have a first degree relative affected with the disease especially if that relative was premenopausal at the time of diagnosis. The risk is less with second degree relatives. [27]

Lichtenstein et al studied the influence of heritable and environmental factors on various cancers using registries of Scandinavian twins. They found that the effect of heritable factors was statistically significant for breast cancer. Their results also supported the general agreement that environmental factors are the predominant contributors to the causation of sporadic cancers.[28]

There are 5 known gene mutations which predispose to breast cancer. BRCA 1, BRCA 2, P53, PTEN and ATM. BRCA 1 and 2, which occur on the long arms of chromosomes 17 and 13 respectively, can cause a high risk of breast cancer and ovarian cancer. Because these genes are so large hundreds of mutations can occur which can make detection of a new mutation difficult. Mutations in P53 predispose to Li- Fraumeni syndrome which as well as early onset breast cancer can cause childhood sarcomas and brain tumours. PTEN mutations cause Cowden's disease where breast cancer is a major feature.

High risk mutations probably account for most families with four or more breast cancer cases, for 20-25% of familial breast cancer risk and 4% of all breast cancers. [21]

In the Scandinavian twin study they found that only a fraction of the genetic effects in their population could be explained by the known gene mutations described above due to their low frequency. This suggests there are other genes yet to be identified.[28]

1.3.9 Ionising Radiation

Exposure to ionising radiation increases risk of breast cancer. There is an increased incidence of breast cancer in survivors of the atomic bombs in Hiroshima and Nagasaki.[29] Women treated with radiation therapy for Hodgkins disease also have an increased risk of breast cancer. This risk is increased the younger the female was at the time of exposure. [30]

1.3.10 Pollution

There is no firm evidence that exposure to pollutants such as pesticides or occupational exposures are related to breast cancer risk. Further studies are also being done to assess the effect of electromagnetic fields, for example, from mobile phone pylons.

1.3.11 Benign breast disease

There is an association between some benign breast conditions and cancer. Dupont and Page showed a five fold increase in risk with atypical hyperplasia. This risk increases to ten fold when there is also a positive family history. [31] At slightly increased risk are those with moderate or florid hyperplasia, papilloma or cysts (1.5- 2 times). [31] Most other benign lesions have no increased risk.[32] The usefulness of these findings as population markers is limited as lobular or ductal hyperplasia with atypia are only found in 4% of breast biopsies and only 15% of women have ever had a breast biopsy.[31]

Factor	Relative risk	High risk group
Age	>10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Before 11
Age at menopause	2	After 54
Age at first full pregnancy	3	First child in early 40s
Family history	>=2	First degree relative when young
Benign breast disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups 1 and 2
Diet	1.5	High fat intake
Body weight:		
Premenopausal	0.7	BMI>35
Postmenopausal	2	BMI >35
Alcohol consumption	1.3	Excessive intake
Ionising radiation exposure	3	Abnormal exposure in young females
Exogenous hormones:		
OCP	1.24	Current use
HRT	1.35	Use for >=10 yrs
Diethylstilbestrol	2	During pregnancy

Figure 2. Established and probable risk factors for breast cancer. Data from McPherson K, Steel CM, Dixon JM. BMJ 321: 624-628. 2000.

1.4

Breast cancer and deprivation

The link between breast cancer incidence, survival and deprivation is well established. As can be seen in figure 2 affluent women are more at risk from breast cancer than those from more deprived backgrounds by about 2 fold.[33] However, women from more deprived backgrounds with breast cancer tend to have a poorer outcome in terms of survival and this has been shown to be true in numerous studies from different countries. [34] Thomson et al found a 10% difference in survival at 10 years between affluent and deprived women in Scotland.[35] Similar results have been found in England, Wales, the US and Finland.[34] The reasons for poorer survival outcomes in women from deprived backgrounds remain unclear. Poorer survival outcomes can be seen with other types of cancer also, such as colon cancer.

Some studies have shown that women from deprived areas with breast cancer have more advanced cancers at presentation either by stage or poorer pathological prognostic indicators (e.g. size, nodal status and grade) [34,36,37], but others disagree. [35,38,39] Thomson et al however, not showing any difference in stage at presentation between affluent and deprived patients, did find that patients from more deprived backgrounds had a higher incidence of ER negative tumours[35] which have a poorer prognosis. [40] This correlates with results from an American study which found a positive relationship between negative ER status, income and education.[41]

If women from deprived areas are presenting with more advanced disease this may suggest that they are less breast aware and are less educated with regards to the disease or that fewer are attending for screening. Stage at presentation may well partly be to blame for poorer outcome, but cannot be the sole reason as some studies have shown poorer outcome with no difference in stage at presentation and those that did still showed poorer survival outcome in deprived women when corrected for stage of disease.[34, 37] A higher incidence of ER negative tumours in women from deprived areas again could only partly explain the difference with an estimated 2.2% five year survival difference being attributable to this. [35]

The question as to whether there is any treatment difference between the affluent and deprived populations, which may make a difference to outcome, has been raised and in Scotland this has been looked into. Thomson's patient population consisted of 21 751 women diagnosed with breast cancer between 1978 and 1987 prior to the introduction of screening and standardisation of cancer care in the UK. The study found that women under 65 with non-metastatic disease were more likely to have breast conservation than mastectomy if they were affluent (45%) than deprived (32%), although over all age groups there was no difference in the type of surgery between deprivation groups. Affluent women were more likely to receive endocrine therapy (65%) than deprived (50%). The differences in treatment seen here may reflect the higher (but not significant) incidence of larger tumours in deprived patients and the higher incidence of ER positive tumours in the

affluent. [35] Also, because breast conservation is no more effective than mastectomy in terms of survival this difference seen should not affect outcome.

A smaller study from the Greater Glasgow Health Board area retrospectively reviewed hospital and general practice records of 821 women who lived in either affluent or deprived areas and were diagnosed with breast cancer in 1992/3.[42] Different aspects of treatment and care were examined including – type of surgery to the breast and axilla, adjuvant radiotherapy, chemotherapy and endocrine therapy and access to care (e.g. delays after presentation). No difference was found in access to hospital care, surgical or non-surgical management between women from affluent and deprived areas.

As previously mentioned survival rates for breast cancer are improving for various reasons including better treatments and increased use of adjuvant therapy, more breast awareness, better prognosis tumours being detected at screening, and improved delivery of care. A recent Scottish study comparing survival in 1987 and 1993 reassuringly showed that survival improvements were similar for both the affluent and deprived groups of women.[8]

In summary, survival differences between women from deprived areas and affluent areas with breast cancer cannot be explained in full by differences in stage of disease at presentation, incidence of ER negative tumours or be due to treatment differences. Other factors suggested which may well be involved include – poorer host responses, co morbidity, adverse nutritional status, less

social support and negative psychological factors in women from deprived areas. At the present time there is little known about the effects of these on breast cancer outcome. They are also factors that would be very difficult to change.

It is known that women from affluent areas are better attenders at screening from data from the Greater Glasgow Health Board breast-screening programme [43] (figure 3). If the attendance at screening of deprived populations was improved this would increase detection of better prognosis tumours in this group which, in turn, would improve survival. The incidence gap between deprived and affluent groups would also be narrowed.

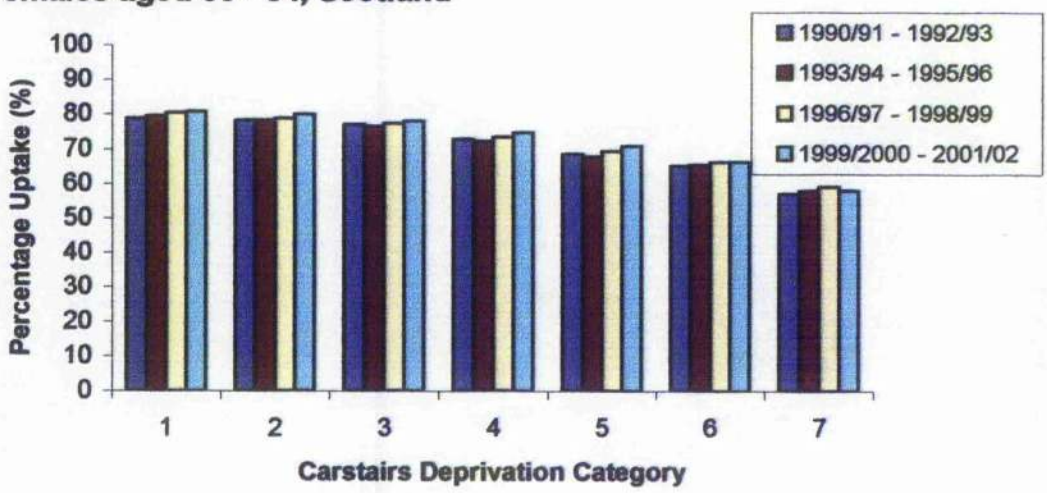


Figure 3. Deprivation and screening uptake in Greater Glasgow Health Board Area. Data from GGHB breast screening programme. Graph from www.isdscotland.co.uk.

If the socioeconomic gap in breast cancer survival is to be closed then further epidemiological study is required to establish the other possible negative factors such as lifestyle and environmental differences. Prevention of the occurrence of the known detrimental factors, which have some effect on survival such as stage of disease at presentation, is also required, maybe by improving education and awareness and improving attendance at screening.

Two studies in Glasgow have looked at deprivation, pathological prognostic factors and stage of disease at presentation. [36,38] Macleod et al found that women from deprived areas did have larger more advanced tumours or metastatic disease at presentation in a population of 417 women. There was no difference in other pathological variables measured (grade, node status). This contradicted the study by Carnon et al who found no differences in stage or pathology between affluent and deprived in a population of 1361 women. In both of these studies substantial amounts of data regarding the tumour pathology was unknown. The studies were also done prior to the full implementation of the Glasgow breast screening programme.

The main aim of this thesis was to clarify the relationship between deprivation and pathological prognostic indicators in the Glasgow area by using a bigger sample of patients with almost complete pathological data and in a population in whom screening was available. Confirmation of the relationship between pathological stage and deprivation should, in turn, spur

on these possible steps for prevention of improving education and attendance at screening in deprived populations.

1.5

Therapy for Operable Breast Cancer

The treatment for primary operable breast cancer comprises of four modalities – surgery, radiotherapy, chemotherapy and endocrine therapy. The aim is to treat the primary tumour, manage the axilla and prevent locoregional and distant metastatic disease.

1.5.1 Surgery to the breast

Surgery to the breast can either be by mastectomy or by breast conserving surgery. Conservation surgery is normally followed by radiotherapy to the rest of the breast tissue. It is well established that conservation surgery and radiotherapy are as effective as mastectomy in the treatment of the primary tumour in selected cases.[44]

The decision on whether to recommend a mastectomy or breast conservation depends on - the size of the tumour in relation to the size of the breast, if the tumour is multifocal or close to excision margins, the age of the patient (young patients have increased risk of local recurrence), the patients own preference and their fitness for surgery/ radiotherapy. Breast reconstruction may be possible after mastectomy and is discussed with all patients prior to surgery.

1.5.2 Surgery to the axilla

As yet there is no consensus on the best way of managing the axilla. Excision of the axillary contents provides information on nodal metastases. This aids the decision on requirement for further treatment with chemotherapy and radiotherapy. It also provides a guide to prognosis [45] (table 1), reduces recurrence in the axilla, and may even cure and improve overall survival.

Survival of women with breast cancer according to lymph node status		Survival of patients according to tumour stage	
	Survival at 10 years	Stage	Survival at 5years
All patients	45.9%	I	84%
Node –ve	64.9%	II	71%
Node +ve	24.9%	III	48%
1-3 +ve nodes	37.5%	IV	18%
>4 +ve nodes	13.4%		

Table 1. Patient survival according to lymph node status and stage breast cancer. Data from "The ABC of Breast Disease". BMJ Publications.

Surgical procedures performed on the axilla include – axillary node clearance (ANC) level I – to lateral border of pectoralis minor, level II – to medial border of pectoralis minor, level III – to the apex of the axilla, axillary node sampling (ANS) and sentinel lymph node biopsy (SLNB).

ANC (level III) removes the entire nodal contents of the axilla and is the only procedure which fully stages and treats nodal disease. It carries with it significant morbidity and therefore the less extensive procedures of ANS (removal of at least 4 individual lymph nodes from the lower axilla) and SLNB (removal of the nodes most likely to be first in the chain draining the tumour) have been performed in an attempt to assess the nodal status of the axilla while causing less morbidity especially in women who are unlikely to have axillary spread. It has been found that the incidence of nodal metastases in patients with tumours of 10mm or less is low. Some studies of tumours of 5mm or less have had an incidence of axillary metastases of 0% [46,47] and some suggest abandoning ANC in these patients. [46,47,48,49] Other studies of tumours up to 10mm have had as many as 27% with positive nodes. [50] At the present time level II ANC is the current preferred practise in the West of Scotland. In the South East ANS or SLNB is performed for small, well differentiated carcinomas.

1.5.2.1 Morbidity from axillary surgery

Several studies have been done to assess the effect of axillary surgery plus or minus radiotherapy (which is given selectively in cases with positive nodes) on arm morbidity.

Arm swelling is very common after axillary surgery and often settles after a few weeks. Lymphoedema may develop months or even years after surgery. Around 75% of cases occur within one year of surgery. The incidence reported varies and can be anything from 13-57%. [51] There is often a precipitating factor such as venepuncture or infection, for example, after a cut. Lymphoedema can also, rarely, lead to secondary lymphangiosarcoma (Stewart-Treves syndrome).

Other morbidities reported with axillary surgery include – reduced shoulder mobility, stiffness, pain, numbness and loss of arm strength.[41, 52, 53, 54, 55] Some have found that these symptoms improve over time [55], but others have not.[52] It has been shown that women with post axillary surgery arm morbidity also have increased psychological morbidity [56] and reduced quality of life [54] associated with it.

Radiotherapy to the axilla along with surgery causes a significant increase in morbidity.[53, 54, 57, 58 - 61] Ververs et al showed a greater than 3 fold increase in the risk of lymphoedema when axillary radiotherapy was given after

surgery.[53] Most would advocate that surgery plus radiotherapy is best avoided if possible.

When compared to ANC less extensive surgery to the axilla causes less arm morbidity. This has been shown to be true for both ANS [56, 59, 60, 61] and SLNB.[64, 65]

1.5.2.2 Axillary sampling

ANS is the removal of at least 4 lymph nodes from the lower axilla, which are detected by palpation by the surgeon at operation. The question of whether ANS can be used as an alternative to ANC and provide the same accurate staging information, reduce recurrence in axillary nodes and improve survival has been looked into in several trials.

Some have found that ANS is not sufficient and suggest that removal of at least 10 axillary nodes [66, 67] or complete clearance [68, 69] is required to provide the most accurate information and reduce risk of leaving involved nodes behind.

A randomised trial of sampling versus clearance after mastectomy by Forrest APM et al followed up patients for a median of 4.1 years. This showed no statistically significant difference in disease free survival or in the time to axillary or breast cancer recurrence between those who had ANS and those who had level III ANC.[70] The majority of patients who had ANS and were

found to have positive nodes were, however, given radiotherapy to the axilla, which unfortunately increases the morbidity.[58, 70] The Clinical Standards Board for Scotland states that at least four nodes must be examined for the axilla to be effectively assessed and that over 90% of patients in Scotland having axillary surgery for breast cancer should have this adequate axillary surgery.[71]

1.5.2.3 Sentinel node biopsy

A possible solution to the dilemma of how to treat the axilla is SLNB. This is when the first node or nodes most likely to drain the tumour are identified (by dye and or radioactive tracer) and removed. The thinking behind this technique is that if the first node in the draining chain does not contain tumour then it is unlikely that tumour will have spread to subsequent nodes. Multicentre randomised control trials are ongoing and will hopefully provide a definitive answer as to whether SLNB can replace ANC. Sentinel node biopsy is used successfully in the treatment of malignant melanoma.

Over the last ten years much work has been done to determine whether SLNB does indeed provide accurate staging in the axilla in breast cancer. In a meta-analysis of 11 trials of patients who had a SLNB followed by ANC the sentinel node was identified in 83.6% with a false negative rate of 5.1% (when the ANC is positive for metasases but the sentinel node is negative). The studies were from surgeons who were experienced in SLNB. It is suggested that surgeons should have a false negative rate of less than 5%

before performing SLNB routinely.[72] There is a learning curve with the procedure and some centres have reported false negatives of up to 13% [73-75]

Higher false negative rates may be more acceptable, however, in patients with small tumours who are clinically node negative and less likely to have axillary spread. An example is given by McMasters et al [76] – In patients in whom the risk of nodal metastases is generally less than 10 –15% - if the false negative rate were 10% only about one such patient in 100 would be assigned too low a stage. ADK Hill et al [73] agree that it is in patients with early breast cancers that this procedure is most valuable. In one study the predictive value in patients with tumours less than 1.5cm was 100% and suggested that SLNB should indeed substitute axillary clearance in patients with small cancers. [77]

In Britain the ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) trial is ongoing. Phase 1 assesses the learning curve with SLNB and recent results have shown that with training, after 40 procedures, a surgeon can achieve a localisation rate of over 90% with a false negative rate of 5% or less.[78] Once trained to this level the surgeon will move to phase 2. This is the randomisation phase comparing SLNB to ANC. Patients with positive sentinel nodes will go on to have radiotherapy or completion clearance. Those with negative sentinel nodes will be followed up. Primary outcomes relate to arm morbidity, quality of life and health economics. Long

term end points will look at axillary recurrence rates in patients who had no further treatment after a negative SLNB.

A secondary aim in this thesis was to assess the incidence of nodal metastases in relation to other pathological prognostic indicators in women with early breast cancers of 10mm or less. This was in an attempt to find a population of women who would be unlikely to have axillary metastases and therefore provide a target population for either omission of axillary surgery altogether or assessment with SLNB.

1.5.3 Other therapies for operable breast cancer

The Early Breast Cancer Trialist's Collaborative Group confirmed that multi agent chemotherapy and/ or endocrine therapy (e.g. tamoxifen) and ovarian ablation improves disease free survival and overall survival in all age groups. [79] Almost all patients receive some sort of adjuvant therapy. The need for adjuvant systemic therapy is determined by assessing the patients' risk of recurrence. This is based on tumour size, ER status, grade, menopausal status and most importantly nodal status.

Present SIGN guidelines suggest the following:

In pre or peri menopausal women

- Women with low risk disease (T1 or 2 node –ve) should be considered for endocrine therapy if ER positive.
- Intermediate or high risk (T3 or grade 3, node +ve or –ve), ER positive disease should be offered chemotherapy or ovarian ablation.
- Intermediate or high risk, ER negative disease should be offered chemotherapy.

In post menopausal women

- Low risk ER positive disease should be considered for endocrine therapy.
- Intermediate or high risk, ER positive disease should be considered for endocrine therapy and/ or chemotherapy.
- Intermediate or high risk, ER negative disease should be considered for chemotherapy (+/- endocrine therapy) if fit.

Some women with large tumours have neo adjuvant chemotherapy to down stage their tumour prior to surgery.

Method

CHAPTER 2

Method

Data has been collected prospectively from five hospitals in the Glasgow area since October 1995 and entered onto the Greater Glasgow Health Board audit of all operable breast cancers database.

Audit forms have been made available to the breast surgeons in each hospital and also to the pathologists dealing with the samples. There are separate forms for the clinical and pathological details of each patient (pages 51-52). This reduces the risk of patients being missed from the audit as the forms are submitted separately. Only patients with operable breast cancers are included in the study, as those who have no surgery will have no pathology results and the main purpose of the database is to provide data from which associations between clinical and pathological findings can be sought.

The database includes all patients with operable breast cancers from Glasgow and East Renfrewshire and some screen-detected patients from Lanarkshire who were treated in Glasgow.

There are an estimated 219,137 females age 30 and above in Glasgow and East Renfrewshire with around 55,381 in the 50-65 screening age group. [80] Around 500-600 new breast cancers (operable and inoperable) are diagnosed every year in the Greater Glasgow Health Board area.[43]

The audit database contained details of 3259 patients who had breast cancers operated on between October 1995 and 2001 (around 550 a year). This is similar to the numbers recorded by Scottish cancer registries when the exclusion of inoperable and the inclusion of screen-detected cancers from out with Glasgow are considered.[43] Although there is no way of determining exactly how many patients may have been missed from the audit this suggests that the dual submission of audit forms has omitted few.

GLASGOW BREAST CANCER PATHOLOGY SUMMARY

Surname

Forename(s)

Date of Birth or Age

C Rec No

PLEASE TICK OR CIRCLE as required

Hospital
GRI WIG Stob VIC SGH RHH Nuffield

Date of sample

Pathology Ref

Supervising Pathologist

Invasive

right ☐ left ☐ bilateral ☐ **TRU-CUT/FNA only ☐**

ductal ☐ **lobular** ☐ **tubular** ☐
medullary ☐ **mucoid** ☐ **cribriform** ☐
mixed ☐ **Other** *(specify)*

Pathological size - greatest diameter (mm)

Pathological Grade:

1	2	3	not applicable	not recorded
☐	☐	☐	☐	☐

Number of lymph nodes **examined:** none received: ☐

Number of lymph nodes **involved:**

	Yes / +ve	No / -ve	not recorded
Nodal Status	☐	☐	☐
Lymphatic Invasion	☐	☐	☐
Blood Vasc. Invasion	☐	☐	☐
ER Status	☐	☐	☐

% ER cells on Immunohistochemistry %

In Situ component:
none ☐ **some** ☐ **extensive** ☐

CONSERVATION ☐ please complete Conservation Section

MASTECTOMY ☐
Pathological removal confirmed?
yes ☐ no ☐
not formally assessed ☐

In Situ Only

right ☐ left ☐ bilateral ☐ **TRU-CUT / FNA only** ☐

		nuclear grade			necrosis
DCIS comedo	☐	1	2	3	yes / no
DCIS non comedo	☐	1	2	3	yes / no
mixed DCIS	☐	1	2	3	yes / no
DCIS LCIS	☐	1	2	3	yes / no

papillary intra cystic ☐ micro - invasive ☐ LCIS ☐

Pathological Size (greatest diameter mm)

CONSERVATION ☐ please complete Conservation Section

MASTECTOMY ☐
Pathological removal confirmed?
yes ☐ no ☐
not formally assessed ☐

Conservation

3 greatest diameter measurements of lumpectomy (mm)
1
2
3

Minimum distance between tumour and lumpectomy edges (mms) not recorded ☐
or
Extends to resection edge ☐

How was completeness of excision assessed? *(tick one only)*

cavity shaving only	☐
cavity shavings & inking of RE + formal assess.	☐
bed biopsies only	☐
CS + BB	☐
inking of resection edge + formal assessment	☐
formal assessment of edge - not inked	☐
not formally assessed	☐

Pathological removal confirmed?
yes ☐ no ☐ not formally assessed ☐

Further Surgery

RE EXCISION ☐ **MASTECTOMY** ☐

Residual disease
none ☐
invasive ☐
in situ ☐
in situ & invasive ☐

Pathological Size (mm)

Pathological removal confirmed?
yes ☐ no ☐ not formally assessed ☐

ALL CASES

Specimen of tumour retained in liquid nitrogen?
yes ☐ no ☐

Comments

Office use only Initials

GLASGOW BREAST CANCER CLINICAL SUMMARY

MANAGEMENT OF PATIENTS WITH PRIMARY OPERABLE DISEASE

INCLUDING THOSE WHO HAD PRE-OPERATIVE (NEO-ADJUVANT) THERAPY

Surname (label) **Forename(s)** **C Rec No** **Consultant in Charge**

Address

Post code

GRI WIG Stob Vic SGH RHH Nuffield

Date of birth **Age**

This patient had breast cancer prior to 1 October 1995

Yes ☐ If 'yes', please register patient details only and return to GGHB.

1st consultation for this clinical episode

Date of GP referral _____ Appointment date _____

Symptomatic ☐
Symptomatic (between screening episodes) ☐
Screening Programme ☐
Not screened - mammographic detection ☐

Menopausal status pre peri post not known

Date LMP *(if applicable)* _____

on HRT never currently or at diagnosis previously not known

Neo - adjuvant

NONE ☐ endocrine therapy ☐ chemotherapy ☐

Surgery

code	R	L	Bi	date (dd mm yy)
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	

1 = localisation biopsy 2 = WLE(or lumpectomy) 3 = cavity shavings
4 = bed biopsies 5 = re excision 6 = mastectomy 7 = axillary clearance
8 = axillary sample

Summary of final surgical management

	R	L	Bi
WLE (or lumpectomy) only	☐	☐	☐
WLE. + axillary clearance	☐	☐	☐
WLE. + axillary sample	☐	☐	☐
mastectomy only	☐	☐	☐
mast. + axillary clearance	☐	☐	☐
mast. + axillary sample	☐	☐	☐

date of definitive surgery _____

Risk Factors DCIS only so not applicable ☐

Grade (1 ,2 or 3)		Nodal Status		A		Pathological Tumour Size (cms)		B		Total A + B
☐	+	☐	=	☐	(	☐	X 0.2)	=	☐	☐ - ☐☐

ADDITIONAL GRADING
tubular, cribriform or mucoid = 1
medullary or lobular = 2

NODES neg = 1
<4 = 2
4 = 3

NPI
3.4 low ☐
3.41 - 6.4 med ☐
>6.4 high ☐

Actual Therapy *(please circle at least one option on each line)*

Radiotherapy no breast flaps axilla

Chemotherapy no CMF anthracyline Other (specify) _____

Endocrine no OA TAM ATAC Other (specify) _____

Clinical Trials

Eligible for clinical trial no yes not known

If 'yes', did the patient enter a trial no yes not known

	entered	refused
UK DCIS		
SCTO pre		
SCTO post		
EORTC		

	entered	refused
high dose chemo		
BASO2		
ATAC		
other (specify)		

Comments

office use only

2.1

Assessment of deprivation and prognostic indicators in all patients with operable breast cancer.

The database was utilised and details of all patients with operable breast cancers between October 1995 and October 2001 were examined. This included both symptomatic and screen detected cancers and patients who had been treated by mastectomy or wide local excision and axillary clearance.

2.1.1 Carstairs Index

The deprivation score was calculated according to the Carstairs index of deprivation. This is a scoring system that uses census data and corresponds to the postcode area where the patient lived at the time of diagnosis.

Vera Carstairs and Russell Morris developed the system in 1981 using the 1981 census data. It is said to be a measure which reflects access to " those goods and services, resources and amenities and have a physical environment which are customary in society." [81] It is a measure of relative disadvantage between populations within small geographic areas, which, in Scotland, can be applied to postcode areas. Each postcode area has a population of around 5000.

The deprivation index takes into account four variables from the census data:

- Overcrowding – proportion of all persons living in private households with a density of more than one person per room.
- Male unemployment – proportion of economically active males seeking or waiting to start work.
- Low social class – proportion of all private households with economically active head with head of household in social class IV or V (based on occupation).
- No car – proportion of all persons in private households who do not own a car.

A score is formulated by standardising each of the four variables so that each has the same influence. The sum of the standardised variables produces the deprivation score (i.e. a measure of socioeconomic status relative to the average for Scotland). Deprivation categories which range from 1-7, 1 being the most affluent and 7 the most deprived are derived from these scores. The intermediate areas contain a mixture of both affluent and deprived households. Deprived areas and affluent areas can lie, geographically very close to each other. (figure 1).

Figure 1. Sherbrooke Avenue, Pollokshields is affluent according to the Carstairs index. Half a mile down the road are the high rise flats on Broomloan Road, Ibrox. Deprivation category 7.

In Scotland 62% of the population are in intermediate areas (deprivation categories 3,4 and 5). Glasgow, however, has a high proportion of deprived households with 30% of the population in the most deprived 7% of the Scottish population.[82] (Figure 2)

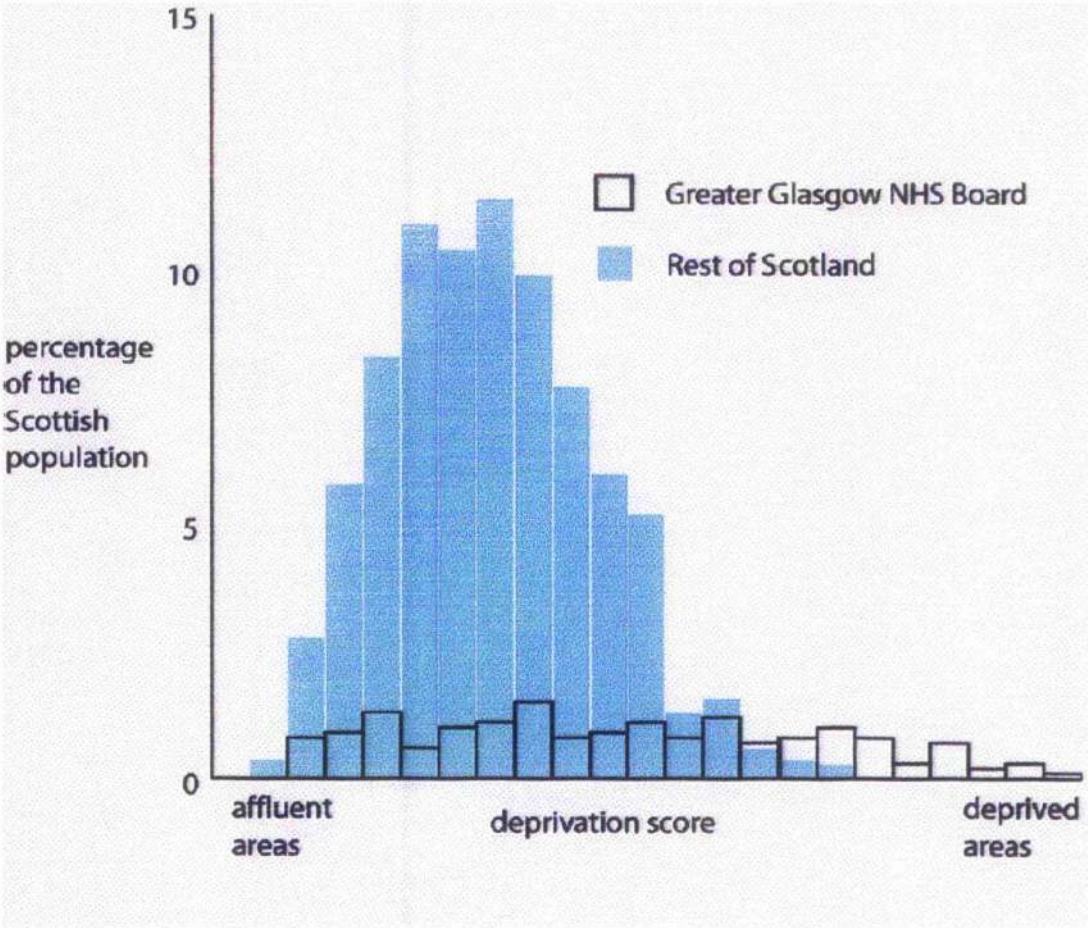


Figure 2. Comparison of deprivation scores between Greater Glasgow NHS Board area and the rest of Scotland. (Graph from Carstairs scores for Scottish postcode sectors from the 2001 census. P McLoone. March 2004)

The scoring system of 1981 has been updated for the 1991 census and again for the 2001 census by Philip McLoone. This shows little change in scores in Scotland between 1981 and 1991 and 2001 although some areas have changed deprivation category. Those areas that did tended to be ones with smaller populations where the data is not so robust.[82] In this study the 1991 deprivation scores were used.

As described in the Scottish economic report of July 2000 [83] the use of the Carstairs index does have its limitations:

Postcode areas are not homogenous and some areas contain a mix of affluent and deprived households and therefore depending on the population of the area some intermediate areas may actually contain more deprived households than a deprived area. Urban areas such as Glasgow, however, tend to be more homogenous.

The choice of indicators from the census is arbitrary and equal weight is given to each. For example car ownership in rural areas where a car is a necessity may not be as useful an indicator of deprivation as in urban areas. Equally, in this day and age, many affluent people choose to live in city centre apartments close to their place of work negating the need for a car. Census data is only updated every ten years, which may cause problems in monitoring health inequalities over this time period.

Despite its limitations McLoone has shown the index to correlate with other socio-economic indicators and to be a good indicator of all cause mortality. Postcode information is the only indicator of socio-economic status on a patient's case record and thus the Carstairs index has been used effectively in many studies of deprivation and health.

In this study we separated patients into three groups. Affluent - deprivation categories 1 and 2, intermediate - categories 3, 4 and 5 and deprived – categories 6 and 7.

2.1.2 Database information

The information extracted from the database included:

Hospital details

Patient unit number

Patient date of birth

Date of surgery

Mode of presentation

Tumour- Size

Histological grade

Oestrogen receptor (ER) status

Oestrogen receptor percentage

Number of nodes excised

Number of nodes involved

The patient date of birth and date of surgery details were used to calculate whether the patient was of screening age at the time of diagnosis and this was related to their mode of presentation. Mode of presentation included symptomatic, screened, symptomatic/ previously screened (i.e. interval cancers) and mammographically detected but not a screening mammogram. Size was measured in millimetres and was either the gross or histological measurement. Tumours were graded 1,2 or 3 according to the Bloom and Richardson grading system. Size, grade and nodal status were used to calculate the Nottingham Prognostic Index (NPI) for each patient.

The relationship between deprivation and tumour size, grade, ER status, Nodal status and NPI were examined. For some of the patients the data was incomplete. As much of this missing data as possible was recovered by reviewing the case notes and pathology records. When the ER status or percentage result was missing the pathology slides were re examined. (Figure 3a and 3b)

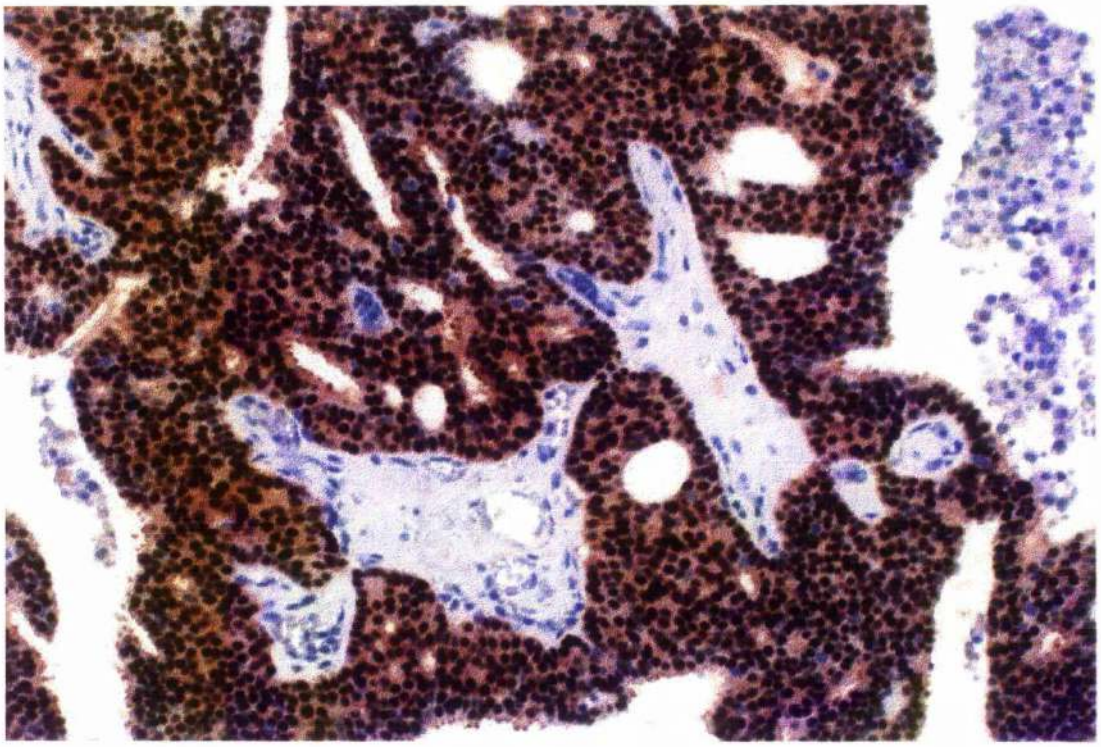


Figure 3a. ER positive breast cancer. ER receptor positive cells stain brown.

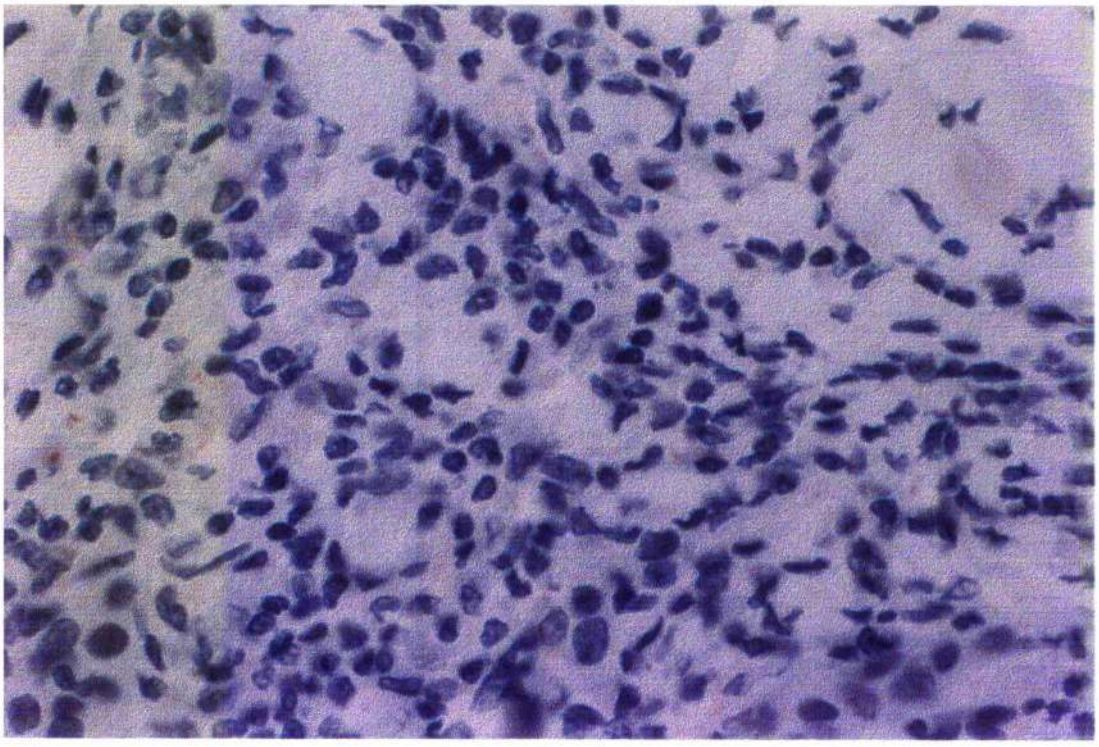


Figure 3b. ER negative tumour. No brown stain.

The variables were examined both with and without the exclusion of patients who had less than four lymph nodes assessed (as it was assumed they may not have had their axillae accurately assessed) or any other missing data.

2.2

Assessment of deprivation and prognostic indicators in tumours of 10mm or less

The database was utilised and the details of patients who had breast cancers of 10mm or less excised and who had deprivation details available between October 1995 and March 2001 extracted. This included patients who were both symptomatic and screen detected. Patients who had less than four nodes excised were excluded from this part of the study as it was assumed that these patients might not have had their axillae accurately assessed.

The effect of deprivation on the above pathological variables was assessed again for this group to see if the findings would be similar even for patients with early cancers. The effect of deprivation on the presence of lymphovascular invasion (LVI) was also looked at. Lymphovascular invasion was defined as invasion of lymphatic and/ or blood vessels.

2.3

Assessment of pathological prognostic indicators in patients with tumours of 10mm or less.

Once again the details of patients with tumours of 10mm or less was examined. All those with tumours excised between October 1995 and March 2001 were included. The relationship between size, grade, ER status, LVI and the presence of lymph node metastases was examined in an attempt to see if there was a particular subgroup of patients with small tumours who are unlikely to have axillary involvement. All patients with less than four nodes excised were excluded.

2.4

Statistical analysis.

Univariate analysis was carried out on each of the variables using the Chi-square test. The Mann-Whitney U test was also applied to nodal metastases in relation to size as it was also assessed as a continuous variable. A multivariate analysis was carried out when assessing the pathological prognostic indicators in early breast cancers using logistic regression (forward stepwise selection).

Statistics were calculated using SPSS for Windows.

Results

CHAPTER 3

Assessment of deprivation and prognostic indicators in all patients with operable breast cancer.

3.1

Introduction

The main aim of this thesis was to clarify the relationship between deprivation and pathological prognostic indicators in the Glasgow area by using almost complete pathological data from a large population in whom screening was available. Confirmation of a relationship between pathological stage at presentation and deprivation should, in turn, spur on possible steps for prevention of improving education and attendance at screening in deprived populations. Other aspects of tumour pathology such as grade and ER status are also assessed in this study to see if women from deprived areas are more likely to have more aggressive tumours.

3.2

Results

There were a total of 3251 patients in who deprivation details were available between October 1995 and October 2001. 598 affluent, 1473 intermediate and 1180 in the deprived group. Deprivation details were missing for 8 patients.

Size was not recorded for 4 intermediate and 9 deprived patients.

Patients in the deprived group were significantly more likely to have larger tumours at operation with 33.3% of affluent, 35.6% of intermediate and 43.4% of deprived having tumours of greater than 20mm ($p<0.001$). (Table 1).

Grade was not available for 9 affluent, 10 intermediate and 8 deprived patients.

The incidence of grade 3 tumours in the deprived group was significantly higher in the more deprived patients. 35% of deprived patients had grade 3 tumours. 30% and 27% of intermediate and affluent patients had grade 3 tumours respectively ($p<0.002$). (Table 2).

ER status was not recorded for 9 affluent, 15 intermediate and 15 deprived patients.

There was a trend for the more deprived patients to have a higher incidence of ER negative tumours ($p=0.016$).

When the ER positive tumours were divided into groups according to ER percentage the deprived patients were less likely to have highly positive tumours ($p<0.01$). (Table 3).

Patients who had less than 4 nodes excised were not included when looking at node status as it was assumed that they might not have had their axilla accurately assessed. This totalled 126 patients. (24 affluent, 50 intermediate and 52 deprived).

The deprived had a significantly higher incidence of node positive tumours ($p=0.043$). 36.8% of affluent, 40.7% intermediate and 42.1% of deprived patients were node positive. (Table 4).

NPI was calculated for all patients in who size, grade and nodal status was available.

Deprived patients had significantly higher NPIs reflecting the higher incidence of larger, grade 3 tumours in this group ($p<0.001$). 45.9% of affluent, 41% of intermediate and 35%of deprived were in the low risk NPI group. (Table 5).

The other variables were examined again excluding patients who had less than 4 nodes examined or any other missing data as for NPI and the significant variables were still found to be so except with node positivity.

From the total of 3251 patients 1685 were in the 50-65 year screening age group (309 affluent, 807 intermediate and 569 deprived patients). Out of this group 60.2% of affluent, 65.5% of intermediate and 56.9% of deprived patients were either screen detected or presented with interval cancers (2.6%, 2.1% and 2.8% of affluent, intermediate and deprived respectively). Significantly less deprived patients were screen detected ($P<0.01$).

Table 1

Size and Deprivation

Size	Affluent	Intermediate	Deprived
1-10mm	152 (25.4%)	317 (21.6%)	200 (17.1%)
11-20mm	247 (41.3%)	629 (42.8%)	463 (39.5%)
21-50mm	188 (31.5%)	483 (32.9%)	471 (40.2%)
>50mm	11 (1.8%)	40 (2.7%)	37 (3.2%)

P<0.001

Figure 1.

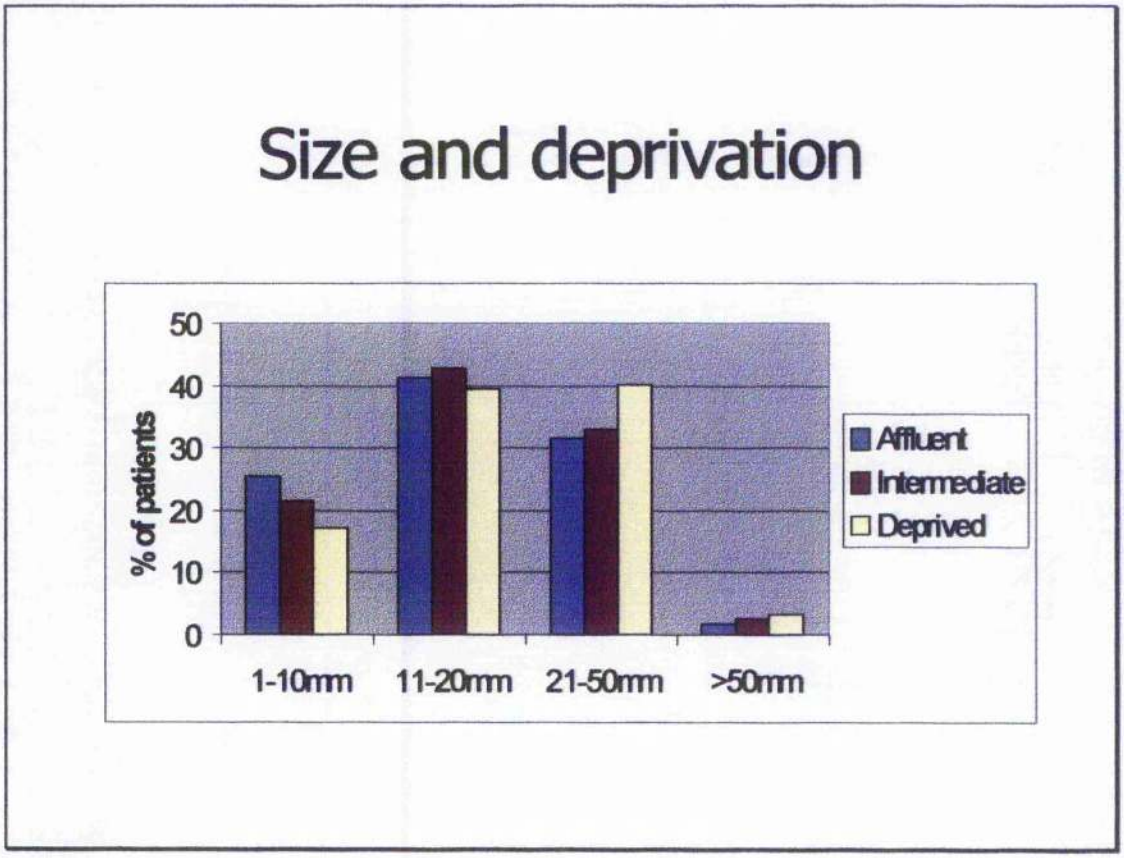


Table 2

Histological Grade and Deprivation

Grade	Affluent	Intermediate	Deprived
1	151 (26%)	344 (23%)	265 (23%)
2	277 (47%)	684 (47%)	493 (42%)
3	161 (27%)	435 (30%)	414 (35%)

P <0.002

Figure 2

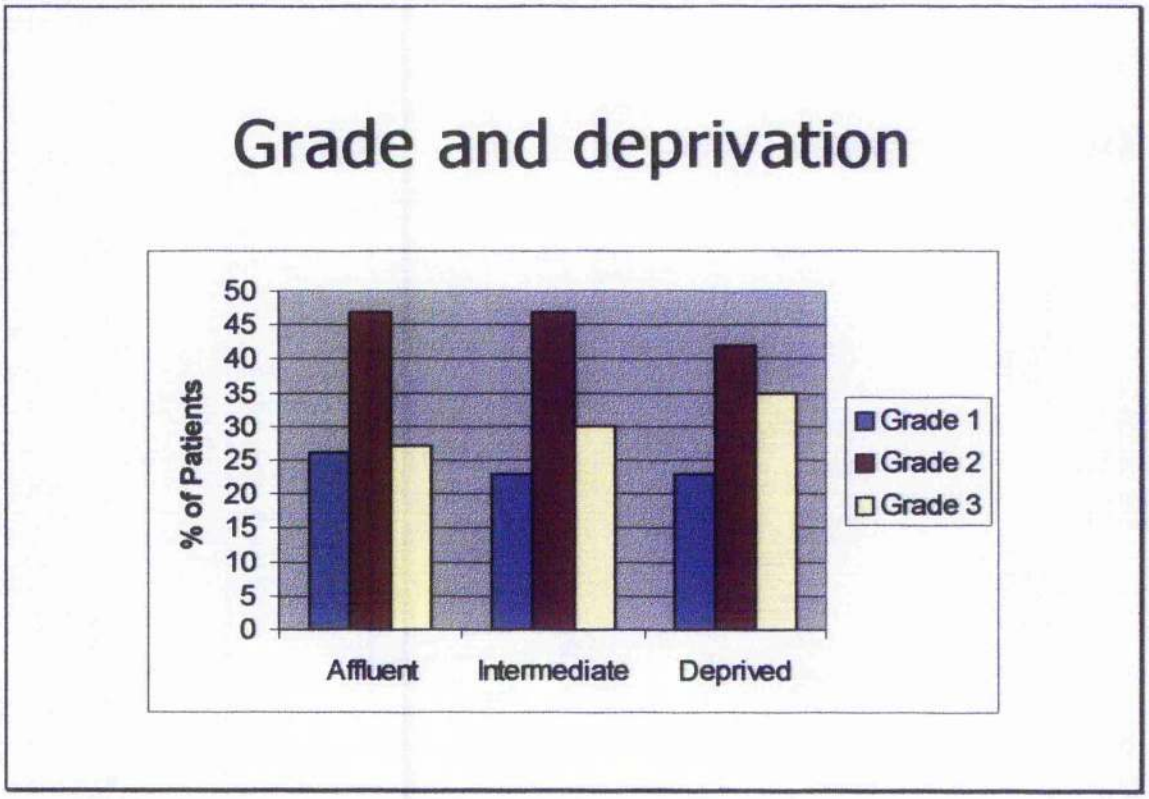


Table 3

ER Status and Deprivation

ER Status	Affluent	Intermediate	Deprived
ER –ve	111 (18.8%)	320 (21.9%)	279 (24%)
5-24%	22 (3.7%)	71 (4.9%)	56 (4.8%)
25-49%	31 (5.3%)	45 (3.1%)	46 (3.9%)
>=50%	425 (72.2%)	1022 (70.1%)	784 (67.3%)

P <0.01

Figure 3

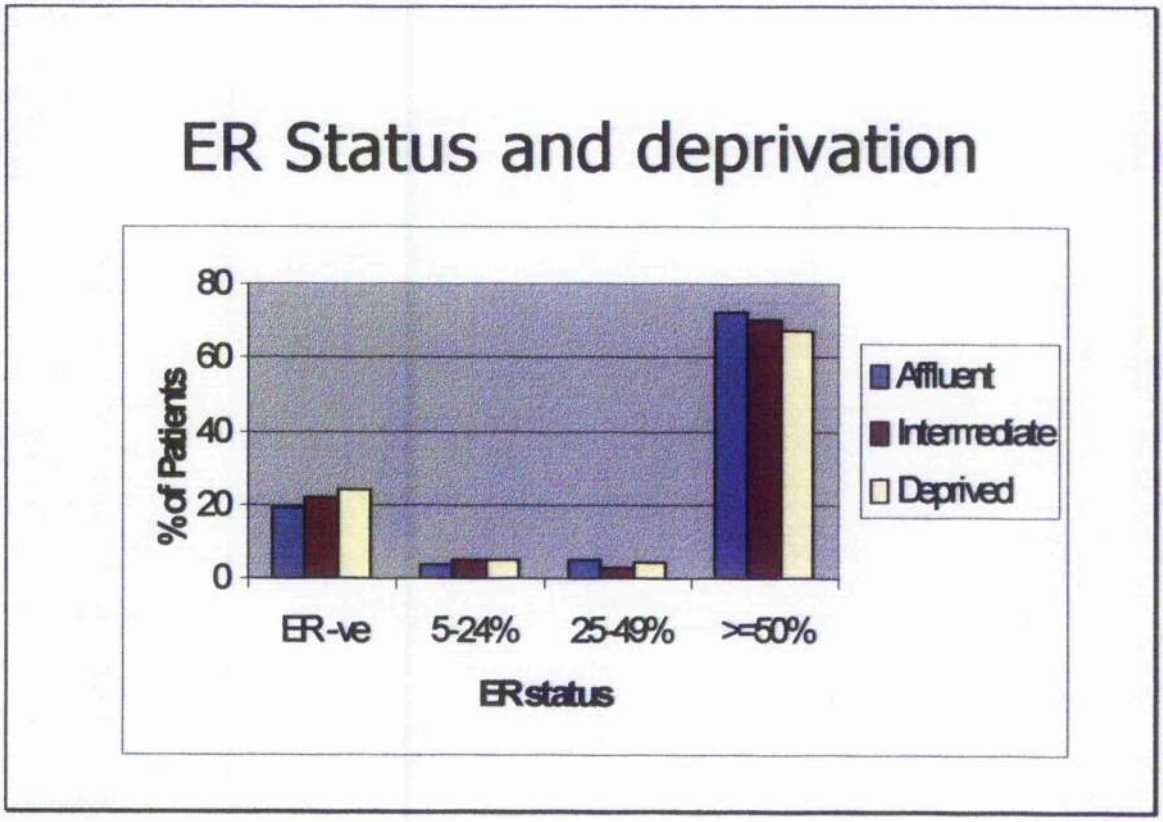


Table 4

Node Status and Deprivation

	Affluent	Intermediate	Deprived
Number	574	1423	1128
Node +ve	211 (36.8%)	579 (40.7%)	475 (42.1%)

P =0.043

Figure 4

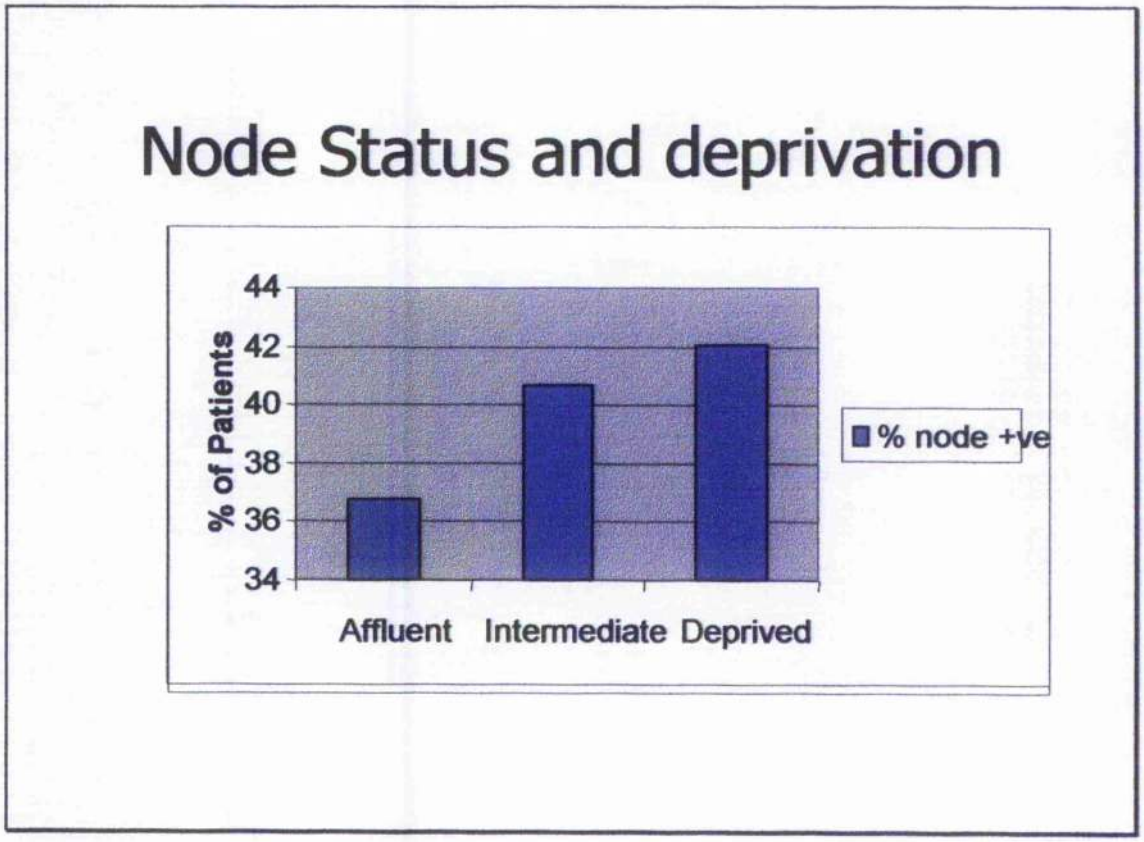


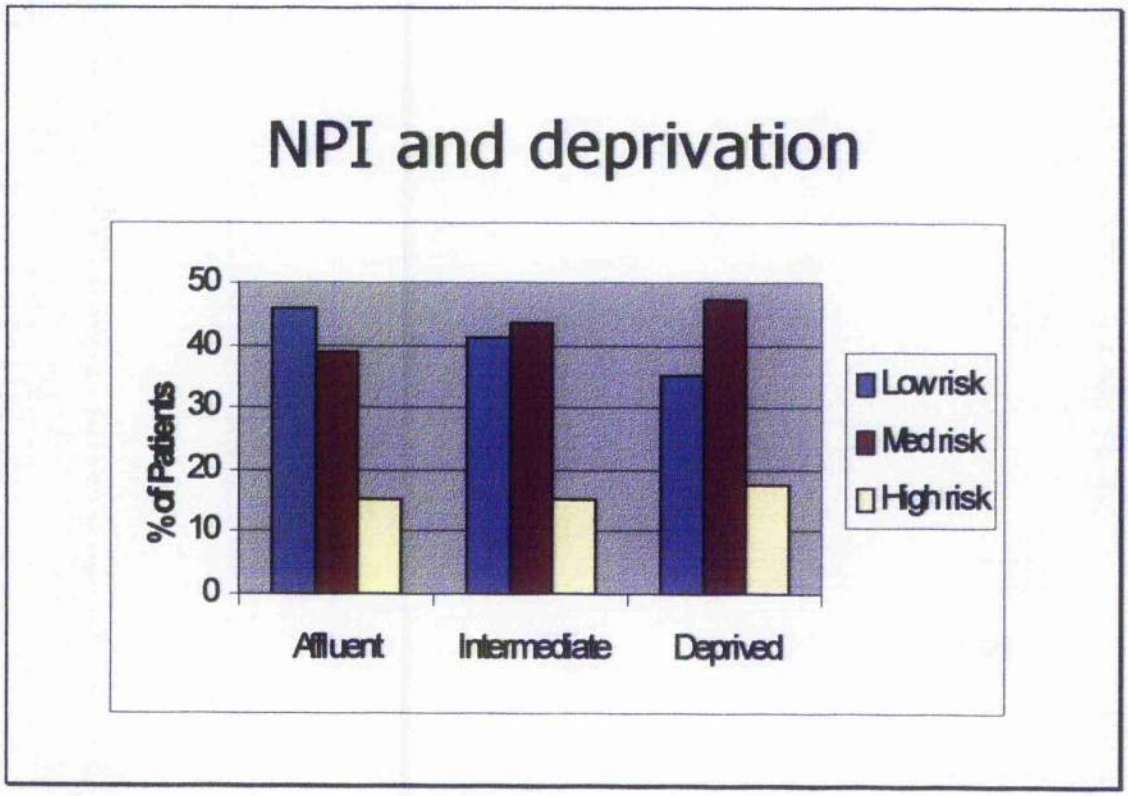
Table 5

NPI and Deprivation

	Affluent	Intermediate	Deprived
Number	567	1410	1115
<=3.4 Low risk	260 (45.9%)	578 (41%)	391 (35%)
3.41-5.4 Med risk	221 (39%)	613 (43.5%)	528 (47.4%)
>5.4 High risk	86 (15.1%)	219 (15.5%)	196 (17.6%)

P<0.001

Figure 5



3.3

Discussion

It is well established that affluent women have a higher incidence of breast cancer than women from deprived areas however women from socioeconomically deprived areas have a significantly poorer survival from breast cancer than women from affluent areas.

This study has found that the poorer outcome of breast cancer patients from deprived areas is multifactorial. Significantly fewer patients from deprived areas have screen-detected tumours and as there is no increase in the interval cancers in this group then this implies that fewer women from deprived areas attend for screening. This would agree with the results from the Greater Glasgow Health Board Breast Screening service data described in chapter 1. Poorer attendance at screening results in deprived patients having significantly larger tumours at operation, which is what this study has confirmed.

However, other factors also contribute to the poorer outcome; women from deprived areas have significantly more high grade tumours and they are also more likely to have ER negative tumours which may be secondary to environmental factors, impaired host responses and co-morbidity. Although deprived patients do not have a significantly higher incidence of node

positivity the differences in size and grade were sufficient to produce a significantly poorer prognosis according to NPI.

This study has demonstrated different results to a previously mentioned study from Glasgow looking at the relationship between socioeconomic factors and pathological prognostic factors. The reasons for this are easily explained.

In the study by Carnon [38] only 1361 patients were assessed of which Grade was only recorded in 54% of patients (99.2% in this study), and oestrogen receptor status in 69%, which although low was high for the time period in question, of patients (98.8% in this study). In their study lymph node status was not recorded in 46% of patients compared to 3.9% in this study and this may have resulted in women being under staged and so under treated.

Similarly, in McLeod's study of 417 patients [36] , grade was recorded in 72.7%, size in 90.2% and node status in 88.5% which again is far less than in this study.

Bias is unlikely in this study because it is a population based, prospective audit with high numbers in each of the deprivation groups. A very small percentage of data was unavailable and similar proportions were missing from each group.

To improve breast cancer survival in patients from deprived areas several areas need to be targeted. Firstly we need to increase breast awareness in patients from deprived areas so that they present earlier but more research is needed to determine the factors leading to the development of the more aggressive grade three, ER negative tumours in these patients.

Chapter 4

Assessment of deprivation and pathological prognostic indicators in tumours of 10mm or less.

4.1

Introduction

The remainder of the study was aimed at women with early breast cancers of 10mm or less. These tumours are less likely to have nodal metastases than larger tumours and generally have a better prognosis. It is these women with early breast cancers that screening aims to detect. The purpose of this section was to assess whether the relationship between deprivation, grade and ER status still existed in women with early breast cancers. Additionally, the relationship between lymphovascular invasion (LVI) and deprivation was looked at.

4.2

Results

In total there were 666 patients. We excluded those who had less than 4 axillary nodes excised. It was assumed that some of these patients might not have had their axillae accurately assessed. Those with ungraded tumours were also excluded. They were ungraded either because they were not ductal tumours or there was too little tissue to assess.

There were 613 patients after exclusions. Deprivation score was available for 608 of the patients. 135 affluent, 293 intermediate and 180 deprived.

We found that patients in the deprived group were significantly more likely to have higher grade tumours (table 1) with 11.1% of affluent, 15.4% of intermediate and 21.7% of deprived patients having grade 3 tumours (p= 0.032). Grade results were available for all included patients.

There was a trend for the more deprived patients to have a higher incidence of ER negative tumours (table 2) with 11.1%, 17.9% and 19.3% of patients in the affluent, intermediate and deprived groups having a negative ER status respectively. This however was not significant (p= 0.073). ER status results were not recorded for 8 patients (2 affluent, 2 intermediate and 4 deprived).

More patients in the deprived group had lymphovascular invasion present (table 3), 13.9% compared to 10.6% and 10.4% in the intermediate and affluent groups (p= 0.3), which reflects the higher incidence of grade 3 tumours. Lymphovascular invasion results were available for all patients.

There was no relationship between node positivity and deprivation (p=0.9) (table 4), nor was there any significant difference in NPI between the groups (p=0.3) although a higher proportion of the affluent group had a low risk NPI (table 5).

Table 1

Grade and Deprivation

Grade	Affluent	Intermediate	Deprived
1	69 (51.1%)	138 (47.1%)	79 (43.9%)
2	51 (37.8%)	110 (37.5%)	62 (34.4%)
3	15 (11.1%)	54 (15.4%)	33 (21.7%)

P = 0.032

Figure 1

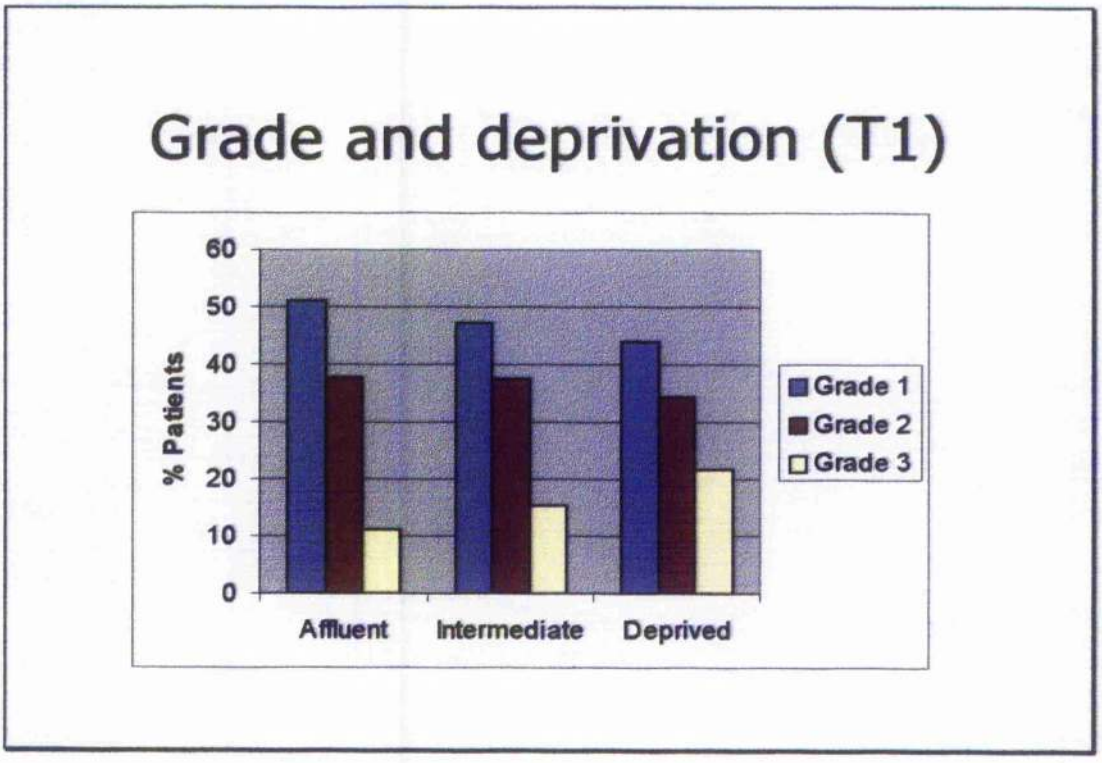


Table 2

ER Status and Deprivation

	Affluent	Intermediate	Deprived
Number	132	291	176
ER –ve	15 (11.1%)	52 (17.9%)	34 (19.3%)

P = 0.073

Figure 2

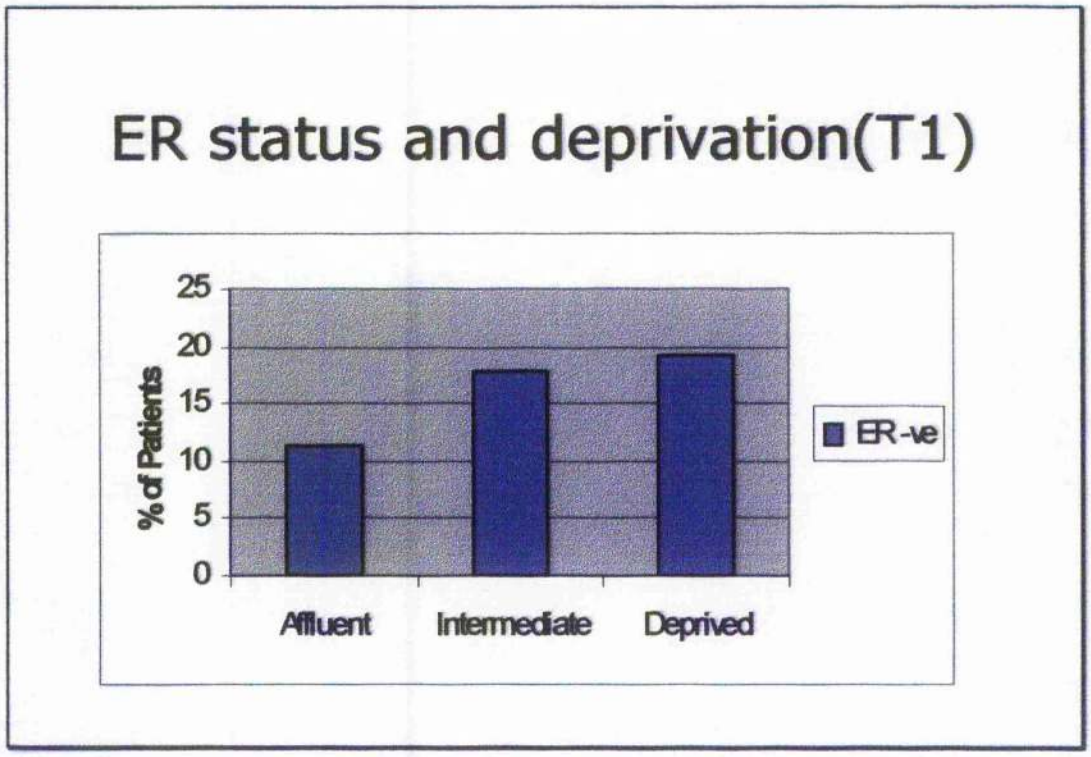


Table 3

LVI and Deprivation

	Affluent	Intermediate	Deprived
Number	135	293	180
LVI +ve	14 (10.4%)	31 (10.6%)	25 (13.9%)

P = 0.302

Figure 3

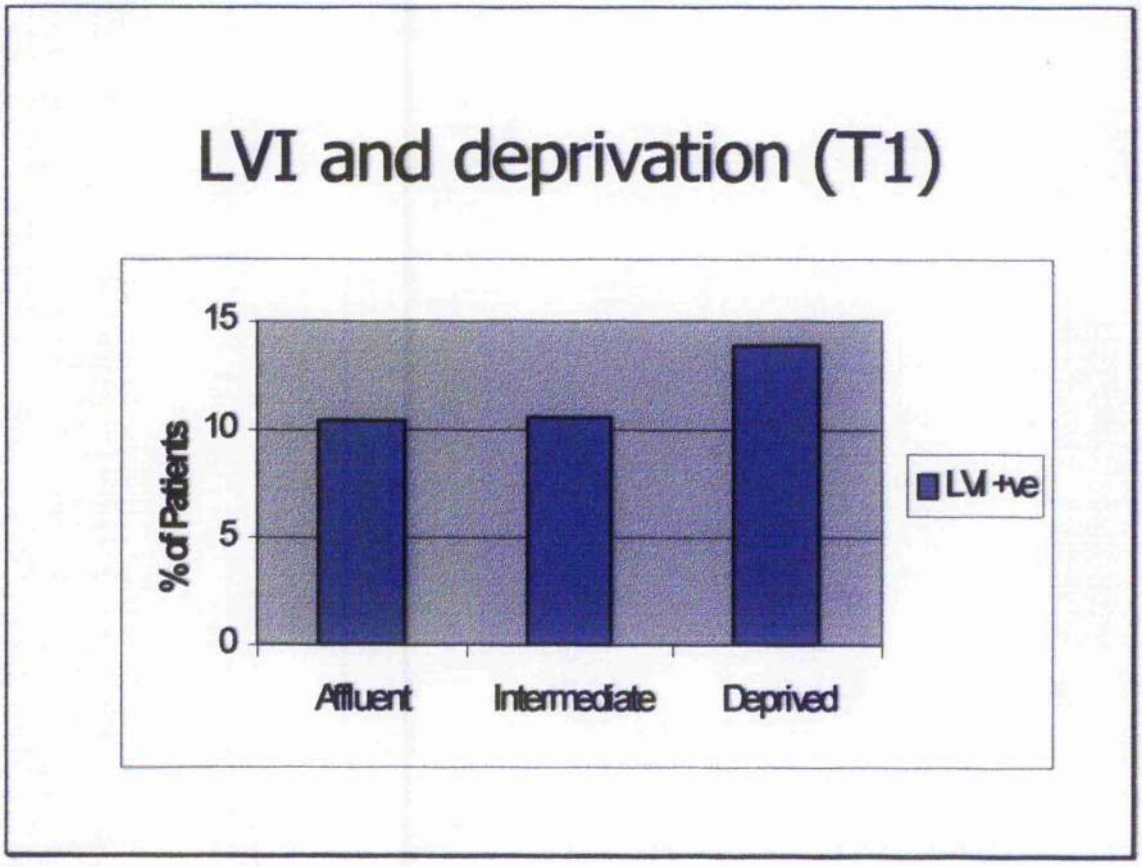


Table 4

Node Status and Deprivation

	Affluent	Intermediate	Deprived
Number	135	293	180
Node +ve	23 (17%)	54 (18.4%)	33 (18.3%)

P = 0.937

Figure 4

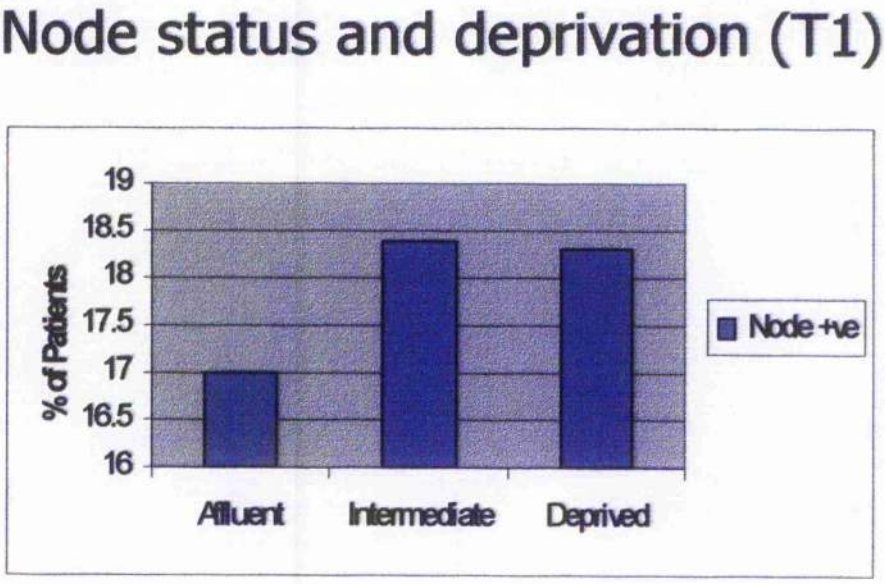


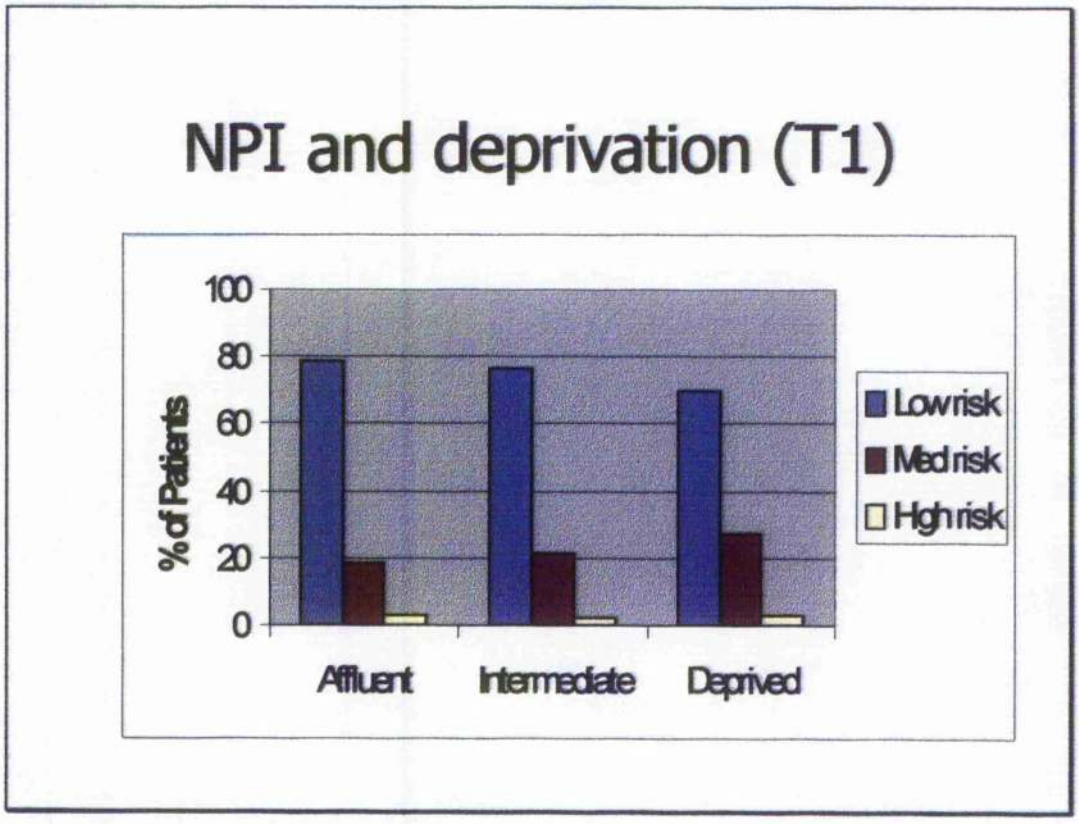
Table 5

NPI and Deprivation

NPI	Affluent	Intermediate	Deprived
<= 3.4 (low risk)	106 (78.5%)	224 (76.5%)	126 (70%)
3.41 – 5.4 (med. risk)	25 (18.5%)	63 (21.5%)	49 (27.2%)
> 5.4 (high risk)	4 (3%)	6 (2%)	5 (2.8%)

P = 0.352

Figure 5



4.3

Discussion

It would appear that early breast cancers in women from deprived areas are less favourable. The relationship between deprivation and grade remains with significantly more deprived women having grade 3 tumours. They also had increased incidences of ER negative tumours and lymphovascular invasion (reflecting the increased number of grade 3 tumours) although this was not significant. As with the more deprived group of women as a whole, there was no significant increase in nodal spread. Unlike the women from deprived areas with tumours of all sizes, the women with early cancers are not at significantly more risk according to NPI than women from affluent or intermediate areas.

Again, in this part of the study, bias is unlikely due to the small numbers with missing data and similar proportions missing in each group. As the patients with known tumours of 10mm or less only were looked at, it is impossible to say in how many patients with these small cancers size was not recorded. There were only 13 patients in the whole 3259 in the last chapter with size not recorded. Therefore, it is likely that the number with tumours of 10mm or less in whom size was not recorded are few with little impact on results.

This, as in chapter 3, suggest that we need to increase breast awareness in deprived populations so that they present earlier when their risk is not significantly different to that of women from affluent and intermediate areas.

Chapter 5

Assessment of pathological prognostic indicators in patients with tumours of 10mm or less.

5.1

Introduction

The aim of this part of the study was to find a population in whom axillary clearance could be avoided. Axillary clearance provides information for staging and prognosis and may also provide local control and even cure as well as aiding in the decision to give adjuvant treatment. However, it carries with it significant morbidity such as lymphoedema, paraesthesia and reduced shoulder mobility. [53, 55] This can have a negative psychological effect on the patient and affect quality of life.[53, 54]

It has been found in other studies that the incidence of nodal metastases in patients with tumours of 10mm or less is low. Some studies of tumours of 5mm or less have had an incidence of axillary metastases of 0% [46,47] and some suggest abandoning axillary clearance in these patients.[46-49] Other studies of tumours up to 10mm have had as many as 27% with positive nodes. [50]

Recently much work has been done into the role of sentinel node biopsy as a means of assessing the axilla for metastases, but there is still a false negative result of up to 13% with this procedure.[73, 74, 75] It has been found that

sentinel node biopsy is more effective in patients at low risk of axillary spread. [73, 75, 77, 84] Sentinel node biopsy is also associated with less arm morbidity.[64, 65]

We wanted to find out which patients with small tumours were least likely to have nodal spread and therefore be spared axillary clearance or provide a target population for assessment with sentinel node biopsy. From the results from chapter 4 it is apparent that deprivation is not a prognostic indicator when it comes to incidence of nodal metastases and therefore it is not included in this section.

5.2

Results

The same 666 patients as in chapter 4 were assessed and again those with less than 4 nodes excised or ungraded tumours were excluded. There was a total of 613 patients after exclusions. 395 (64%) were screen detected. The majority, 461, were ductal carcinomas. The rest were 36 lobular, 88 tubular, 2 medullary, 10 mucoid, 4 cribriform, 7 mixed and 5 other (e.g. phylloides). No distinction between types of tumour was made in this study.

Of the 613 patients 26 (4%) had only 4 nodes examined. That is 4% of the patients had axillary sampling rather than clearance. In one of these patients all 4 nodes were positive suggesting some diseased nodes may have been left behind.

In total 111 (18.1%) of the patients had positive nodes. Of these, 49 (44%) had only one positive node. 19 (17%) had two positive nodes, 10 (9%) had three and 33 (30%) had four or more nodes positive.

There was a trend for the larger size tumour to have an increased incidence of positive nodes with 13.4% of T1a and 19.2% of T1b tumours being node positive. This difference was not significant ($p= 0.18$), but when we looked at size as a continuous variable it was a significant indicator of nodal spread ($p< 0.001$). (Table 1).

A higher grade was also a significant indicator of nodal spread with 11.4% of grade 1, 21% of grade 2 and 31.3% of grade 3 tumours having positive nodes ($p< 0.001$). (Table 2)

We looked at the influence of size within each grade and as can be seen in the table 3 the trend for the larger size tumours to be more likely to have metastases is still there in grades 1 and 2, but not for the grade 3 tumours. This finding is most likely because of the smaller numbers in this group with only 16.2% of patients having grade 3 tumours. (Table 3)

The most important indicator of lymph node spread was the presence of lymphovascular invasion ($p<0.001$). 54.3% of tumours where lymphovascular invasion was present were node positive. (Table 4)

The influence of lymphovascular invasion within each grade was also examined. There was a higher incidence of positive nodes when lymphovascular invasion was present and this was true for each grade. It was not significant in the grade 3 group and again this is most likely because of the smaller number in this group. (Table 5)

When we looked at ER status, as a single variable, those with ER negative tumours were significantly more likely to have axillary metastases than those with ER positive tumours ($p=0.038$). 16.5% of ER positive tumours and 25.7% of ER negative tumours were node positive. (Table 6) ER status was unrecorded for 8 patients.

However, when we corrected the ER status for the other three variables with a multivariate analysis it was no longer a significant factor. (Table 7)
The most important predicting indicator was lymphovascular invasion with a greater than five fold increase in risk of having positive nodes if lymphovascular invasion was present. Next was grade with a relative risk of 1.51 for each step up in grade and then size with a relative risk of 1.15 for each millimetre increase in size.

Low risk tumours are those of grade 1 without lymphovascular invasion. In total 9.5% of grade 1 tumours without lymphovascular invasion of 10mm or less were node positive. Of those 5mm or less 5.7% was node positive. None of the patients with grade 1 tumours of less than 5mm without

lymphovascular invasion had axillary metastases, although the number in this group was very small. (Table 8)

Table 1

Metastases and size.

	Total	T1a	T1b
Number	613	119 (19.4%)	494 (80.6%)
Node positive	111 (18.1%)	16 (13.4%)	95 (19.2%)

P= 0.18. Size as a continuous variable P< 0.001

Figure 1

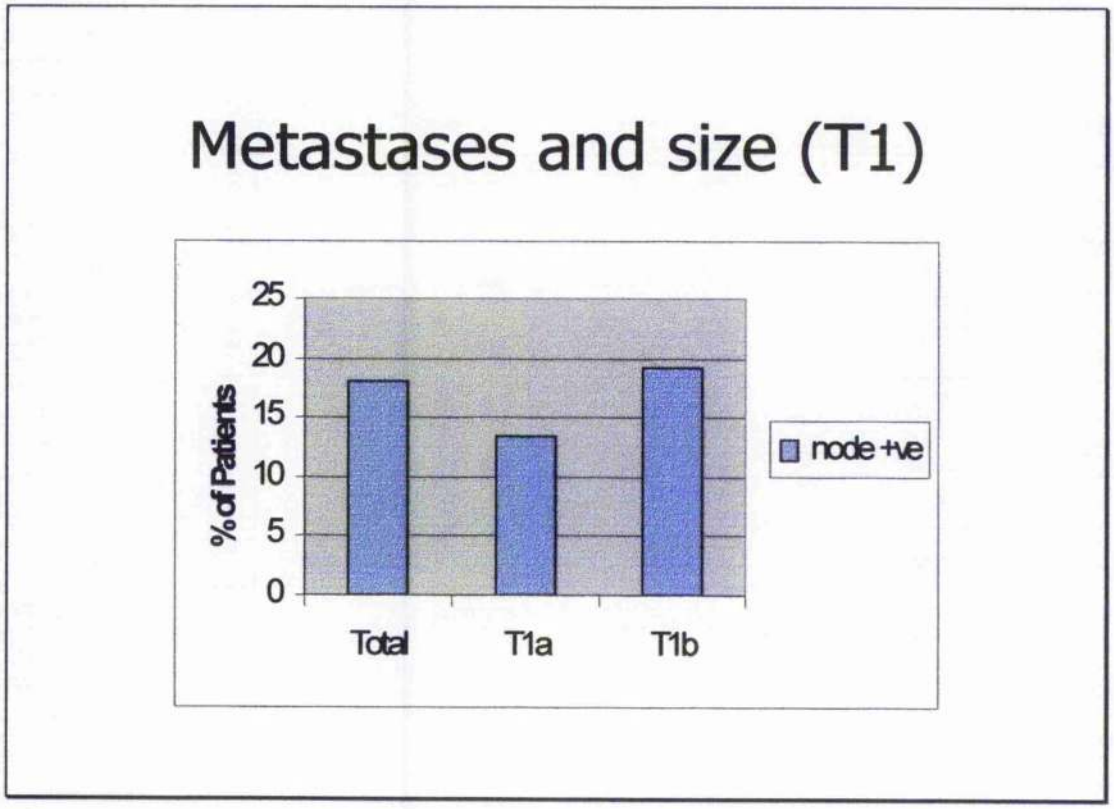


Table 2

Metastases and Grade

Grade	1	2	3
Number	289 (4.1%)	225 (36.7%)	99 (16.2%)
Node +ve	33 (11.4%)	47 (21%)	31 (31.3%)

P< 0.001

Figure 2

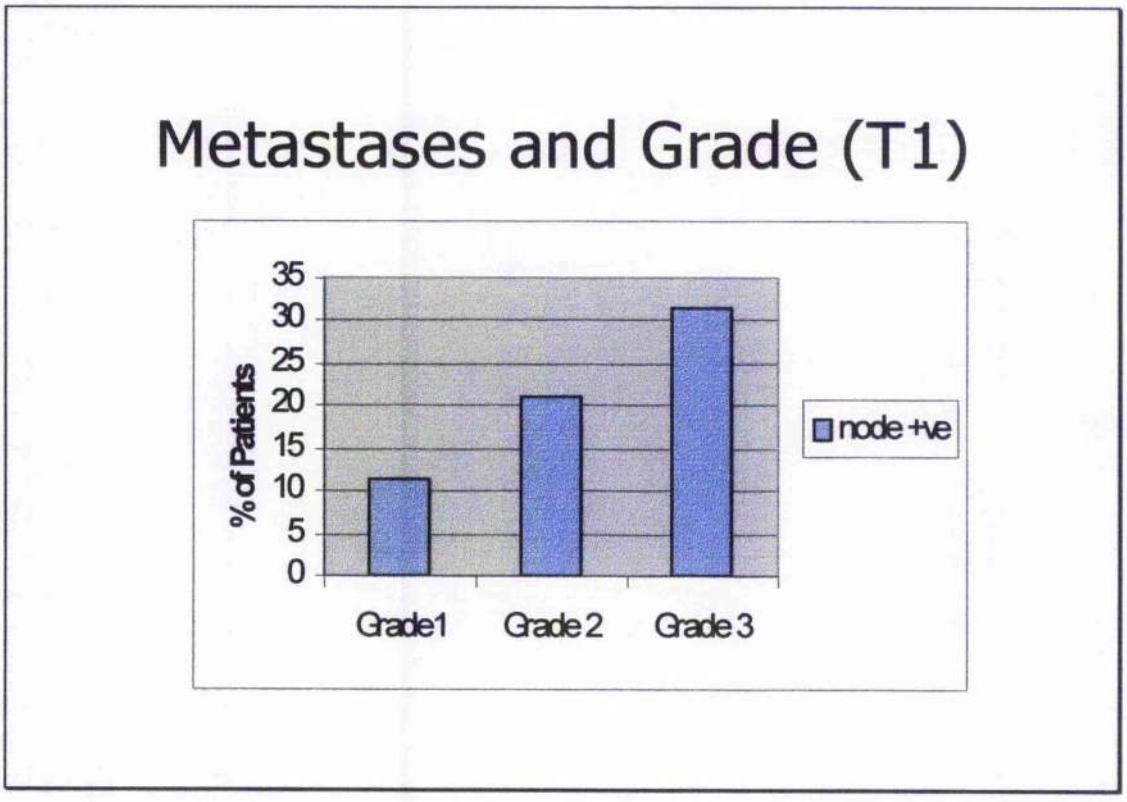


Table 3

Metastases, Size and Grade

	Grade1		Grade 2		Grade 3	
Size	T1a	T1b	T1a	T1b	T1a	T1b
Node +ve %	5.7	12.7	11.1	23.3	40.9	29.5
	P= 0.002		P< 0.001		P= 0.227	

Table 4

Metastases and Lymphovascular invasion (LVI)

	LVI –ve	LVI +ve
Number	543 (88.6%)	70 (11.4%)
Node +ve	73 (13.4%)	38 (54.3%)

P< 0.001

Figure 4

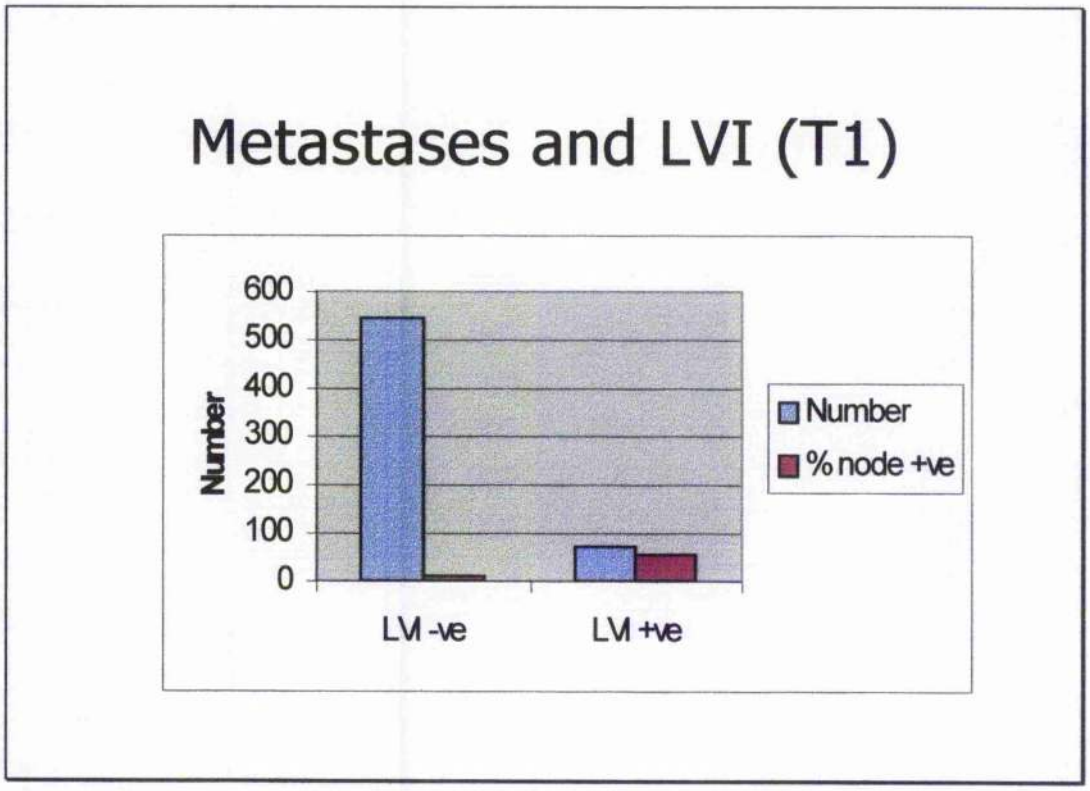


Table 5

Metastases LVI and Grade

	Grade 1		Grade 2		Grade 3	
LVI	-ve	+ve	-ve	+ve	-ve	+ve
Node +ve %	9.5	50	14.6	69.2	26	43.3
	P< 0.001		P< 0.001		P= 0.103	

Table 6

Metastases and ER status

	ER +ve	ER –ve
Number	504 (83.3%)	101 (16.7%)
Node +ve	83 (16.5%)	26 (25.7%)

P= 0.038

Figure 6

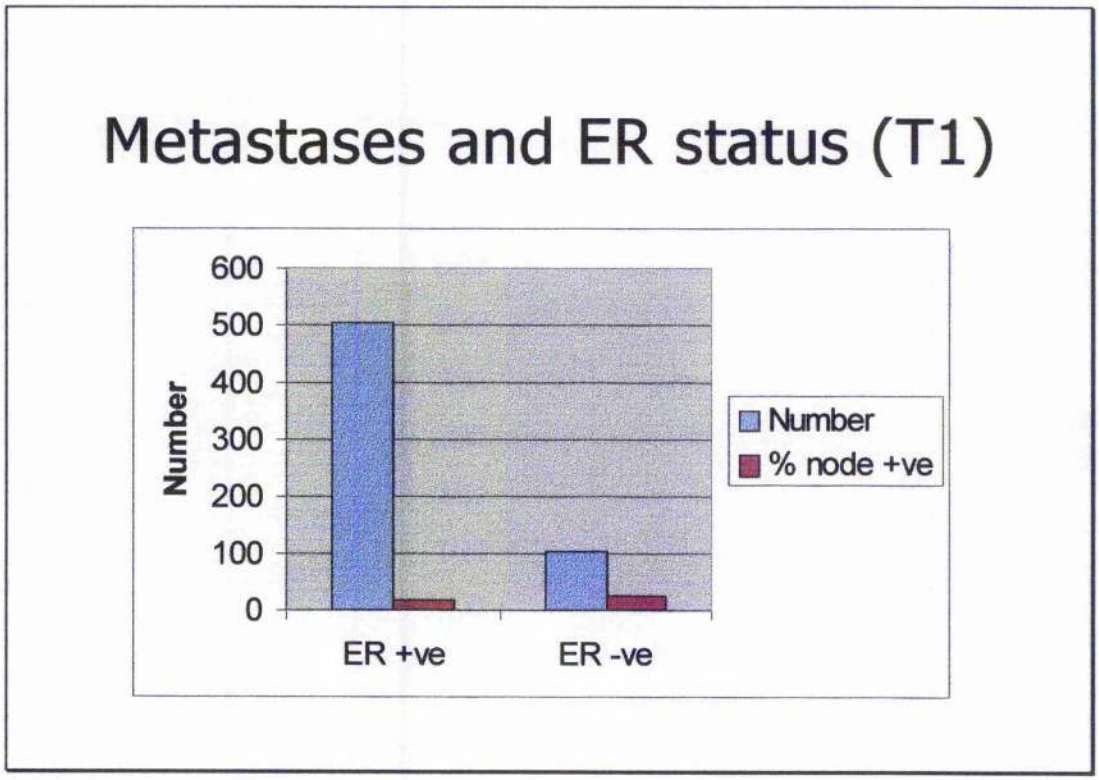


Table 7

Significant Variables (multivariate analysis)

	Relative Risk	95% CI	Significance
LVI	5.4	3.07 – 9.48	P< 0.0001
Grade	1.51	1.12 – 2.05	P= 0.007
Size	1.15	1.03 – 1.29	P= 0.01

Table 8

Low Risk Tumours (grade 1, LVI –ve)

Size	< = 10mm	< = 5mm	< 5mm
Number	275	53	20
Node +ve	26 (9.5%)	3 (5.7%)	0

5.3

Discussion

It is well recognised that axillary dissection, especially when coupled with radiotherapy, causes significant arm morbidity.

Over the years many studies have been performed in an attempt to find a way to reduce arm morbidity by means of reducing the extent of surgery to the axilla. Some would favour omitting axillary surgery altogether in patients with breast cancers of 5mm or less. This study has shown an incidence of nodal metastases in tumours 5mm or less of 13%. Clearly omission of axillary clearance cannot be decided on tumour size alone. This has shown that the risk of nodal metastases is multifactorial with the presence of LVI being the most important predictor next to tumour grade.

Size was a less important predictor being significant only as a continuous variable and not when divided into T1a and T1b groupings suggesting that choosing a cut off for surgery at 5mm on its own may be meaningless. None of the variables assessed in this study alone could accurately predict nodal spread. Only a very small subgroup of 20/613 patients with low risk tumours (grade 1, LVI negative, less than 5mm) who were all node negative could be identified. Certainly, these patients are unlikely to have axillary disease, but for them to avoid axillary dissection the procedure for all early breast cancers would have to be two stage to identify this small group of patients. The

primary tumour would have to be excised to assess pathology. Once this was known the axilla would have to be dealt with appropriately requiring a second anaesthetic. This is because assessing grade or presence of LVI can be very difficult from core biopsy alone.

This study suggests that there are no patient subgroups in whom axillary surgery can be omitted safely on the basis of the tumour pathological predictive factors described.

Lymph node status is an important predictor of survival outcome even in cancers of 1cm or less. [85] Axillary node status needs accurate assessment not only to aid in the prediction of survival outcome, but also to assist in the decision to give adjuvant therapy, which should be considered for all patients with positive nodes no matter how big the tumour.

It is possible that axillary clearance could be avoided in patients with early breast cancer if the node status could accurately be predicted by other means such as sentinel lymph node biopsy (SLNB). In some areas in the world this procedure is being performed almost routinely despite the fact that there are no results for randomised controlled trials or with regards to long-term outcome.

There is a learning curve associated with SLNB and with it can be a significant false negative rate. [86] Higher false negative rates may be more acceptable,

however, in patients with small tumours. Furthermore according to Weiser et al [84] patients with tumours of 1cm or less without LVI who are found to have micrometastases in the sentinel node have a low risk of non sentinel node metastases and therefore may not require completion clearance.

In summary, the results would suggest that axiliary surgery should not be omitted even in patients with very low risk cancers. These patients may provide a population whose axillae are best assessed by SLNB.

As in the previous chapter, bias is unlikely due to the completeness of the data. Because this study looked only at cancers which had been operated on and size was measured as the pathological size it is impossible to say from this audit if any patients with small tumours had distant metastases and did not undergo operation.

General Discussion

Chapter 6
General Discussion

Over the past few decades the incidence of breast cancer in Britain and the rest of the world has been increasing. Despite this, survival has been improving due to improved treatments, better delivery of care and the introduction of screening which has served to identify women in the high risk age groups with disease at its early stage.

Research has shown that there is no one cause of breast cancer, but that there are many risk factors which, in combination, may make some women more prone to the disease. Environmental factors probably play a huge role and are most likely responsible for the difference in incidence of breast cancer seen in different areas in the world.

A similar effect can be seen between women from different backgrounds within the same country or even the same city. Women from affluent backgrounds have a higher risk of breast cancer than those from deprived areas. This could be due to them having different genetic backgrounds and environments as well as more risk factors, for example, more may stay longer in education and have families later or differences in diet. It is unlikely that the reasons for this difference in risk will be easy to identify and even more difficult to change.

Even though affluent women are more at risk of the disease, women from deprived areas are more likely to die from it. This study has shown that in the Glasgow area women from deprived backgrounds are more likely to have bigger, more aggressive tumours at presentation, which in turn, leads them to have a poorer prognosis according to NPI. They are also more likely to have ER negative tumours which can be more difficult to treat as they do not respond to hormone therapy and carry a poorer prognosis.

The findings in this study may certainly explain, to some extent, why these women have a poorer outcome. What is not clear is why women from deprived areas should have these more aggressive tumours. Again, the reasons are almost certainly multifactorial. Genetic as well as lifestyle differences and a higher incidence of co-morbidity leading to impaired host responses are likely to play a role. Environmental factors such as pollution and radiation as well as other as yet unidentified factors may contribute but this has not been proven. It is difficult, however, on driving through Glasgow not to notice how close in proximity some deprived areas can be to affluent areas. They may be only a few hundred meters apart. What environmental factor can affect one of those areas and not the other?

It is obvious that further epidemiological research on a huge scale will be required if an answer to the socioeconomic differences in breast cancer is to be found.

The improvement in breast cancer survival is seen in both affluent and deprived women and probably reflects the standardisation of care over all areas. The outcome gap between affluent and deprived still exists and as it is likely that this is mainly due to unknown factors out with our control then we can only narrow the gap by attempting to improve on factors which we do know about. These are the factors described in this study.

Differences in grade and ER status between affluent and deprived again cannot be explained easily. The fact that women from deprived areas have larger tumours at presentation, as found in this study, and that there was no difference in incidence of interval cancers in this population suggests that fewer deprived women are attending for screening. This would agree with figures from the Glasgow Breast Screening Programme (chapter 1, figure 3). It is this area, therefore, which initially should be targeted to try and reduce the survival differences between affluent and deprived. It has also been shown in this study that deprived women with early breast cancers are not at significantly higher risk according to NPI than other women. Thus if they are managed early survival differences should narrow further.

To improve attendance at screening, amongst other things, will require better education with regards to the service and breast awareness as well as encouragement from general practitioners. Recently there has been a television campaign warning people of the signs of colorectal cancer. As breast cancer is the most common cancer in women should this too be

advertised more widely on the media with regards to the importance of attending screening?

The second part of this study focused on women with early breast cancers who are those most often picked up at screening. Many of these women do not have axillary metastases and undergo axillary clearance, which for many of them will turn out to have been unnecessary and lead to morbidity.

Recently many studies have looked into the possibility of using sentinel node biopsy as a method of assessing the axilla. After training In the procedure it can be performed very accurately with low false negative results especially in women at low risk of axillary metastases.

From this study it can be seen that even women with small tumours of 10mm or less can have axillary disease although the incidence is reasonably low (18%). There is not a population of women in whom it could be risked to omit axillary surgery altogether. It would seem, however, that these women with small tumours could provide a target population for assessment of their axilla by SLNB especially if the tumour is negative for LVI, which is the most important predictor of axillary spread. 44% of women in this study who had positive nodes only had one node with metastases. The chances are that this would be the sentinel node which would be removed at the procedure thus potentially it could also cure. There are ongoing studies attempting to find accurate predictors of non-sentinel node spread if the sentinel node is

positive to try and avoid the need for completion clearance or radiotherapy in these patients. Since there are no single accurate predictors of axillary spread itself, it seems unlikely there will be one factor that could predict spread to non-sentinel nodes.

There are no long term outcome results for the procedure as yet and results of randomised controlled trials such as the ALMANAC trial are awaited. SLNB is performed routinely In many countries. In Britain the procedure is only performed as part of a trail at the present time. It looks promising that in the near future this will be the procedure of choice for trained breast surgeons here for women with small cancers.

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Chapter 7

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