The impact of socio-economic factors on outcome from breast cancer

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Presented for degree of MSc (Med Sci)

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September, 2006

Abstract

For many years it has been recognised that a deprivation gap exists in breast cancer. While incidence is highest in affluent women, deprived women seem to do worse. The reasons for this are not clear. Differences in tumour pathology or hormone receptor status may be responsible. Geographical differences exist in breast cancer survival and treatment by a specialist breast surgeon also seems to improve prognosis. However, many of these studies were done before the introduction of breast screening, which has undoubtedly changed the way in which breast cancer is diagnosed and treated. This thesis analyses the pathological and treatment data on a group of women who were diagnosed in Glasgow between 1996 and 2001, after breast screening as well as multidisciplinary teams had been established. The presence of a deprivation gap had previously been described in Glasgow. The aim of this thesis is to identify if there remains a survival gap between affluent and deprived women and to what extent treatment and pathology are responsible.

All women treated for primary operable invasive breast cancer in Glasgow between 1995 and 1998 were analysed. In total, 1717 women were treated. Median follow up was just over 6 years. Overall 5 year survival was 80.4%. There was a trend for worse survival in the most deprived group (83.9% vs. 77.8% in the most affluent group) but this was not significant. Interestingly, deprived women had larger, node positive tumours and were more likely to be symptomatic but this did not affect survival. On multivariate analysis age, Nottingham prognostic index (NPI) and oestrogen receptor (ER) status were independent predictors of survival. These results suggest that the deprivation gap may no longer exist in Glasgow. While, follow up may not be long enough to identify a deprivation gap, the introduction of standardised treatment by multidisciplinary teams may have had an impact on narrowing the deprivation gap.

Surgical treatment for breast cancer can be by mastectomy or conservation surgery. The differences in survival suggest that perhaps surgeons themselves are treating affluent and deprived women differently. Women diagnosed between 1996 and 2001 were analysed to see if surgical treatment varied between affluent and deprived women. 3419 women were eligible for conservation surgery by their tumour size.

46.4 % underwent conservation surgery, the remainder had a mastectomy. Deprived women were significantly more likely to have a mastectomy ($p<0.001$). However, they had larger tumours that were more likely to be symptomatic. On multivariate analysis, deprivation was related to likelihood of having a mastectomy. Deprived women were therefore treated appropriately and it was tumour size that determined surgery not biased treatment. There was, however, significant variation in mastectomy rate between hospitals suggesting that there is a lack of consensus on the best surgical management of primary operative breast cancer.

It has previously been shown that affluent women not only have a higher incidence of breast cancer but they are also more likely to have ER positive disease. ER positive breast cancer is more likely to respond to hormonal therapy and is less likely to recur, resulting in a better prognosis. It is also associated with nulliparity, late age at first birth, late menopause and HRT use. All of these reproductive factors have increased in the last 20 to 30 years but more so for affluent women. Two cohorts of patients were compared. The first were diagnosed 1980-1988 and had ER status determined by ligand binding assay, the second, diagnosed between 1996 and 2001, had ER determined by immunohistochemistry. The proportion of ER positive tumours rose from 50.1% in the early cohort to 79.3% in the late cohort. This increase was independent of age, deprivation or hospital of diagnosis ($p<0.001$). The proportion of ER positive breast cancers increased for all deprivation categories but there was no significant difference between the most and least deprived. Some of this rise is due to changes in the methodology of determining ER status; however, this does not explain all of the difference. Increases in the prevalence of the actiological factors for ER positive breast cancer are, in some part, responsible.

Differences in the host response to the tumour may be responsible for survival differences. The systemic inflammatory response, as measured by C-reactive protein (CRP) to cancer predict prognosis in a variety of solid tumours. In addition, deprived people appear to have a raised "background" level of inflammation which may contribute to survival differences between rich and poor. CRP and IL-6, its inflammatory cytokine, were determined in a group of 194 patients both pre and post operatively. All patients were followed up for a median of 52 months. CRP was not related to deprivation. There was no difference in survival between deprivation

categories. However, pre-operative CRP (p=0.03) but not post operative CRP independently predicted survival independent of age, deprivation, NPI, ER status and HER2 status. Combining pre and post operative CRP as a score gave a powerful predictor of survival (p=0.001). This suggests that patients with a raised background inflammatory response combined with the response to the tumour itself do especially badly.

There no longer appears to be a deprivation gap in survival for women with breast cancer. Differences in surgical treatment do, however, exist but this appears to be due to bigger tumours in deprived women. Hormonal, aetiological factors for ER positive breast cancer have increased overall for all women but this does not seem to contribute to socioeconomic differences in tumour pathology. The systemic inflammatory response may play a role in predicting survival from breast cancer but it does not appear to differ between social classes. Improvements in diagnosis and delivery of treatment must therefore play the largest role in narrowing the deprivation gap.

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Acknowledgments

The completion of this work has involved the support of many people. Thank you to Prof Tim Cooke for supervising this thesis, his invaluable support in conceiving the studies and giving feedback on the results was greatly appreciated. His helpful comments on the drafts of this thesis were gratefully received.

Thank you to Prof David Hole for his help with the statistical analysis.

Thanks also go to Dr. Donny MacMillan for his help in the conception of the idea for Chapter 4 and help with the data analysis.

Prof Robin Leake and Dr Elizabeth Mallon were generous in sharing their data on the ligand binding assays and immunohistochemistry assays for oestrogen receptor status. The biochemical analysis was performed at Glasgow Royal Infirmary, the help of Prof Naveed Sattar and the staff in the biochemistry department was gratefully received.

Finally, thank you to Dr. Harry Burns and Eileen Kesson at Greater Glasgow Health Board for sharing the data from the Greater Glasgow Breast cancer audit and their ideas for the data analysis.

Introduction

It is well known that breast cancer is the most common female malignancy and 1 in 9 women in the UK will be diagnosed with breast cancer at some point in their lives. Extensive media coverage adds to public awareness of the disease. However, what is not so well known are the inequalities that exist in the disease. While affluent women are more likely to develop breast cancer it is socio-economically deprived women that are more likely to have a worse outcome. Many reasons for this have been suggested but they have never been fully elucidated. Much of the work that was done to examine reasons for these differences was done on populations of women in the pre-breast screening era. The introduction of breast screening has changed not only the way that breast cancer is diagnosed but it has also changed the pattern of the disease. This makes it time to revisit whether the deprivation gap still exists and to what extent pathological and treatment factors influence it.

Glasgow is one of the most socio-economically deprived urban areas in the UK. A rapid increase in industrialization followed by a rapid decline in industry has left Glasgow with high levels of socio-economic deprivation which makes it ideal for studying the effects of deprivation on cancer incidence and survival.

Like the rest of the world the incidence of breast cancer in Greater Glasgow is high and on the rise. Between 1990-1999 incidence was 108.5/1000, 000 (data from ISD Scotland) and overall incidence level has risen by around 25 % since 1980 (fig1). Part of the reason for the rise in breast cancer incidence can be attributed to the introduction of breast screening in 1990. From the graph below a sharp increase is seen between 1990 and 1993 when the prevalent round of screening was completed. However, the incidence has continued to rise after this, so breast screening does not explain this trend.

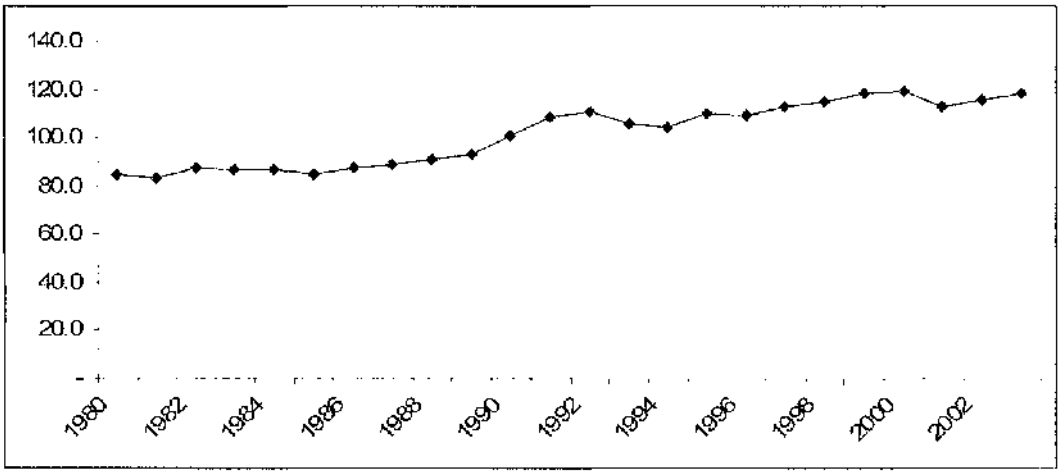


Fig 1: Trends in incidence: Age-standardised incidence rates per 100 000 person-years at risk (European standard population) for the period 1980-2003

Although the incidence of breast cancer is high, and continuing to rise, breast cancer survival is good at around 80% 5-year survival (1996 – 1998 data from Scottish Cancer Intelligence Unit). Mortality has improved significantly over the past 20-30 years. The introduction of breast screening has contributed to this but undoubtedly improvements in the diagnosis and treatment of breast cancer have also made their contribution. Despite these general trends in breast cancer incidence and mortality, persistent differences exist in outcome between countries and within the same country.

1. Breast cancer incidence and mortality worldwide

1.1 Worldwide trends in Incidence.

Broadly speaking, breast cancer is a disease of the Western world. World-wide, it has the largest incidence in the most developed countries (Data from CANCER*Mondial,* web-page address: http://www-dep.iarc.fr/), with the USA and the Netherlands having the highest incidence. The lowest incidence occurs in developing countries, with Mozambique and Haiti having the lowest incidence (Data from CANCER*Mondial,* web-page address: http://www-dep.iarc.fr/). The variation in incidence between the most and least affluent countries is at least 10-fold. Studies of migrants to affluent countries have shown that the reasons for this wide variation in incidence are likely to be environmental rather than genetic. Comparisons of Asian

women (an area of low incidence) who have migrated to the USA have shown that their offspring have a greater risk of breast cancer (1). Part of this reason may be due to the effect of mammographic screening. In affluent and highly resourced countries not only does the presence of screening increase the number of cancers detected it also results in better registration of breast cancer diagnoses. However, it appears that environmental factors inherent in the "Western lifestyle" are the main contributing factors.

The introduction of breast screening in the USA and Europe resulted in an increase in incidence as the prevalent round was completed (fig. 2). However, even before the introduction of screening incidence was increasing. In fact, while increases were being seen in the countries that had introduced screening there were similar marked rises being noted in countries that did not yet have a screening programme. Not only that, but increases were noted across all age groups, not just the screening age group (2). More recently, there does appear to have been a plateau in incidence although the level of incidence is higher than before the introduction of screening(2). While, improvements in cancer registration may have contributed to this phenomenon, breast screening does not explain why there should have been an increase in the non-screened populations. Changes in the incidence of risk factors for breast cancer may therefore play a role.

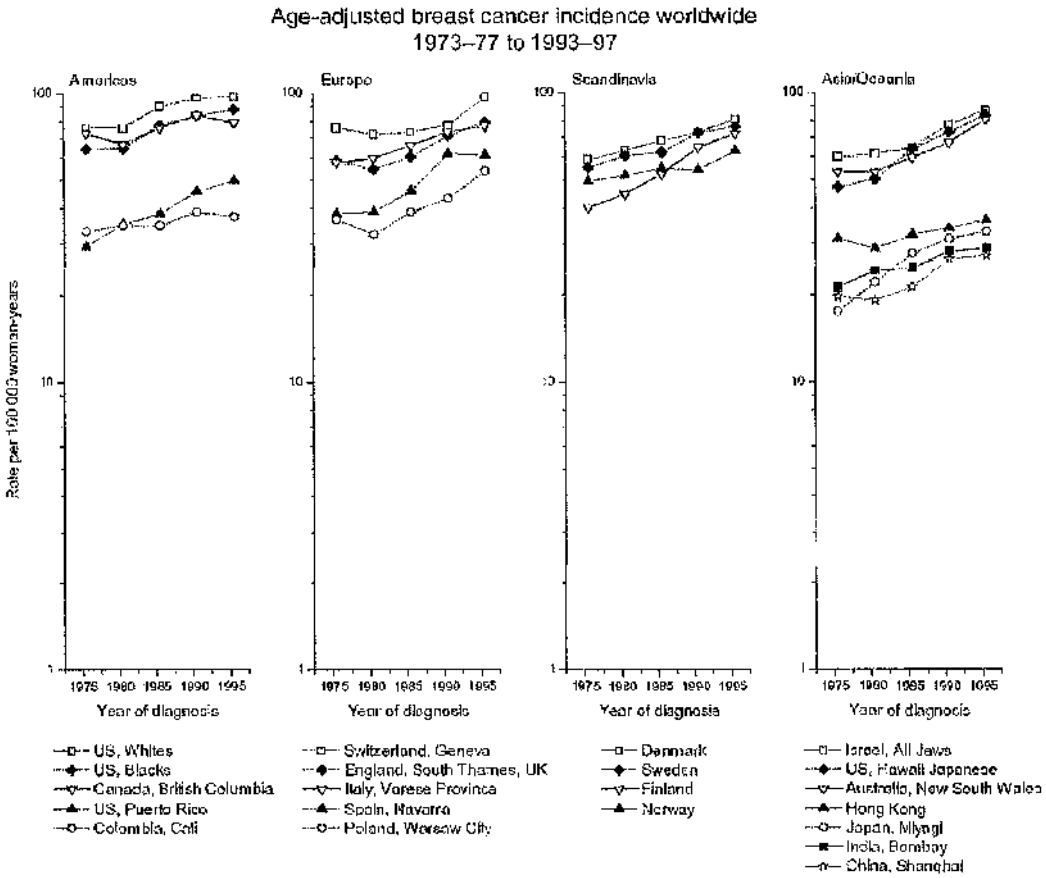


Fig 2: Age-adjusted breast cancer incidence rates for US black and white women generated from nine SEER registries representing 9.5% of the population. Incidence data for all other countries abstracted from IARC Cancer Incidence in Five Continents (1973-77 to 1993-97) (3)

In Asia, where there is a relatively low incidence of breast cancer, there has been a rapid rise in incidence, which is more marked than in other regions of the world (fig. 2). The majority of countries do not have a breast screening programme (with the exception of Japan) so this increase in incidence must be due to changing patterns of risk factors and environmental exposure (3). In developing countries there also appears to be an increase in incidence. There is a relative scarcity of high quality cancer registry data, however, what data there is, confirms that rising incidence of breast cancer is not peculiar to the Western world. In addition, it appears that the rate at which incidence is climbing is faster in developing countries, with the fastest rate of increase in the urban dwellers of those countries (2).

Thus development and the adaptation of the Western lifestyle seem to be more important than any genetic susceptibility. The risk factors which increase exposure

to endogenous oestrogen that are associated with breast cancer (early age at menarche, nulliparity, late age at first birth, low parity and late menopause) are more prevalent in the Western world and are also associated with improved socio-economic status (4). The use of hormone replacement therapy may also have a role to play as could obesity and reduced physical activity.

Interestingly, within countries incidence differs by socio-economic status. In all countries, regardless of whether they are developed or developing, affluent women have a greater incidence of breast cancer. Studies from Finland (5), the Netherlands(6), Denmark (7), the USA as well as in the UK (8;9) have all consistently shown that affluent women are more likely develop breast cancer. This adds weight to the argument that there is an environmental rather than a genetic reason for why women tend to develop breast cancer and, whatever this environmental influence is, it is likely to be associated with affluence.

Although it appears that increased breast cancer incidence is associated with the affluence and adaptation of the Western lifestyle, there does appear to be differences in the aetiology of breast cancer between different countries. If the patterns of incidence are further examined by comparing similar age groups of Japanese and American women, they are different (fig. 3). In the USA there is a sharp increase in incidence with age which continues to rise after the age of 50 but at a somewhat slower rate. In Japan, however, there is a similar increase in rate of increased incidence but at the age of 50 incidence plateaus and even goes down with age (see fig. 3) (3). A similar pattern is seen in women from the USA and Denmark with oestrogen receptor (ER) negative breast cancer (3). This suggests that the type of breast cancer most prevalent in Japan is different to that in Europe and the USA. ER negative breast cancer may therefore be more associated with deprivation while ER positive breast cancer is associated with affluence and adoption of the Western lifestyle. In addition, geographical variation between countries suggests that genetic factors may also play a part.

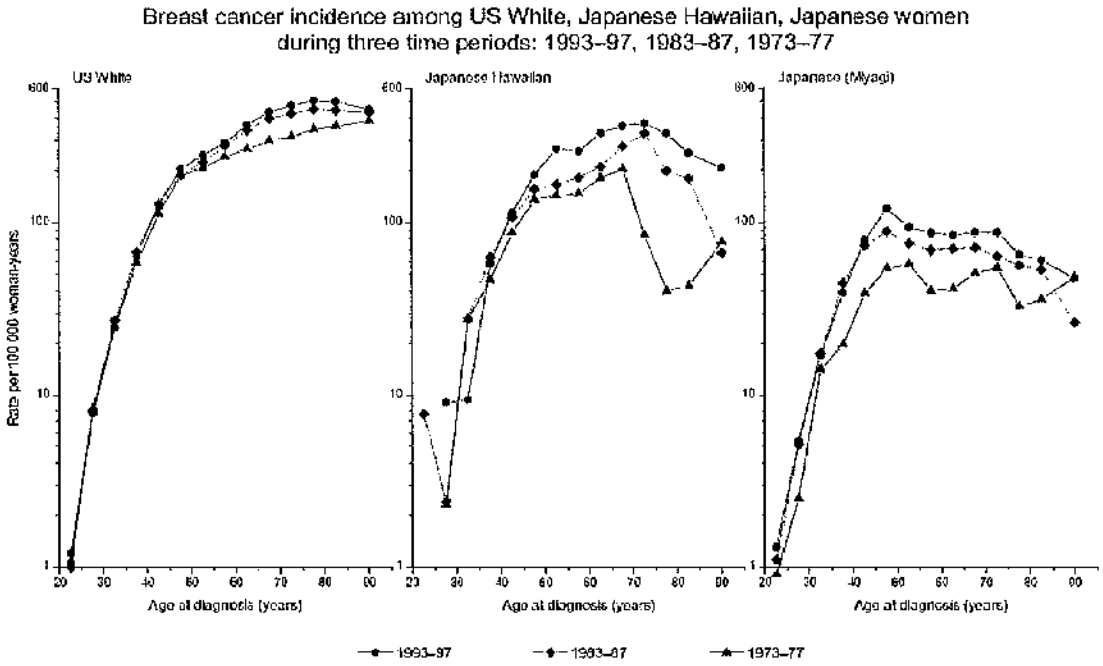


Fig 3: Age specific incidence rates for US white women generated from nine SEER registries. Rates for US Hawaiian Japanese and Japanese (Miyagi) women abstracted from IARC Cancer Incidence in Five Continents (1993-97, 1983-87, 1973-77)

1.2 Worldwide trends in survival

Despite the high incidence in the West, it is women from developing countries who have a higher mortality from breast cancer. In the USA, Australasia and Northern Europe breast cancer mortality has consistently been in decline since at least the early 90's and this decline is most marked in the over 50 age group (2). Prior to this (from the 1950's onwards) there had been a general increase in mortality. These improvements are in part due to the introduction of breast screening, however, similar trends are seen in the younger age groups so breast screening does not explain all of these changes. Conversely in countries which had a relatively low rate of breast cancer incidence in Eastern Europe, for example the Russian Federation, Estonia, Romania and Hungary, there has been as increase in mortality (2). Again, epidemiological data for developing countries is somewhat sparse due to the lack of cancer registries. However, from what is available, it is evident that mortality has remained the same and in some places increased (2).

The reasons for these wide variations are not immediately obvious. Part of the reason may be that women from developing countries present with advanced disease and they are less likely to be diagnosed at breast screening because there are no breast screening facilities. However, improvements in breast cancer mortality are seen throughout all age groups in affluent countries suggesting that breast screening does not explain all of these temporal trends. The availability of treatment may also explain some of the differences in mortality, however, even within developing countries there appears to be a difference between how well affluent and deprived women do following a breast cancer diagnosis. This leaves differences in environmental and aetiological factors as the remaining explanation for survival differences (see later). It is interesting to note that the pattern of incidence of breast cancer in Asia (see fig 3) with a decline in later age mirrors that of ER negative breast cancer in the USA (2). The explanation for the difference in mortality may therefore be that women from less developed countries are developing ER negative tumours.

2. Breast cancer incidence and mortality in Scotland

The incidence of breast cancer in Scotland is similar to the rest of Europe. While incidence is higher in Scotland compared with Southern Europe, it is lower than USA. However, mortality from breast cancer in Scotland is worse than USA (fig 4). Similar to the rest of the world, the incidence and mortality for breast cancer in Scotland varies with socio-economic status. It has been consistently shown that, independent of stage at presentation although deprived women in Scotland have a lower incidence of breast cancer than affluent women, they do consistently worse than more affluent women(8;10) (fig 5). In particular the levels of deprivation in the West of Scotland are higher than the rest of the country (11) which makes Scotland a good place to study the effects of deprivation on breast cancer incidence and mortality.

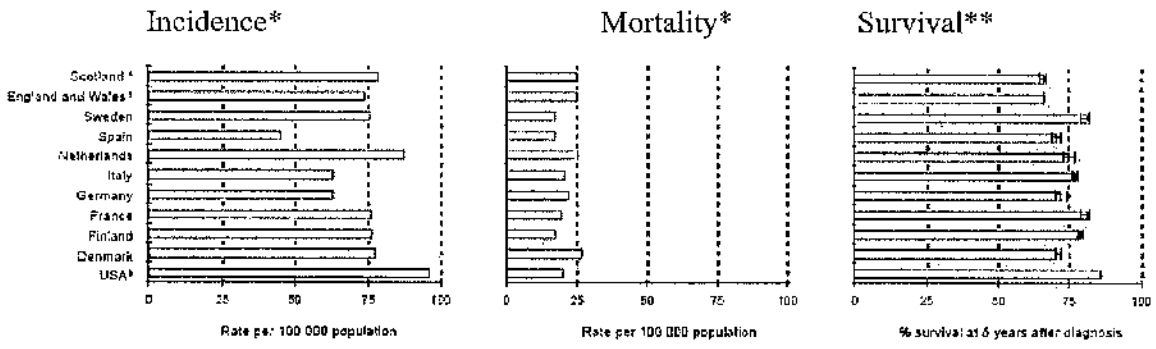


Fig 4: International comparison of incidence, mortality and survival from breast cancer with 95 % confidence intervals (12)
*Age-standardised rates per 100, 000 person years at risk (world standard population)
**Relative survival at 5 years, patients diagnosed 1985 – 1989

2.1 Measuring Deprivation in Scotland

Deprivation and health are intrinsically linked. Indices of deprivation are important in analysing cancer registries for the effect of deprivation on health. They are also used to determine the allocation of resources by local, regional and central government to health boards and primary care. Several indices are in routine use. The commonly used scores are the Townsend score, favoured in England and Wales and the Carstairs score, favoured in Scotland. Both are based on various census variables, to a varying degree, however the Carstairs score was designed specifically to determine deprivation in Scotland (13).

The Carstairs and Morris score focuses on material deprivation in individual geographic localities. Census based variables for postcode sectors are determined and given a score. Postcode sectors are postcodes that are the same apart from the last two characters. The scores were originally described by Carstairs and Morris as a measure to reflect access to "those goods and services, resources and amenities and of a physical environment which are customary in society" (13). The 2001 version of the Carstairs score used the following variables: overcrowding (the proportion of people living in private households with a density of more than one person per room); male unemployment (the proportion of economically active males seeking or waiting to start work); low social class (the proportion of people in private households with an economically active head with head of household in social classes IV or V); ownership of a car (the proportion of people in private households which do not own a car) (14). These variables were selected because they have been shown to be highly correlated with one and other. The resulting score is then divided into 7 deprivation categories or "dep cats." The dep cat is therefore a measure of the population's relative material deprivation rather than an individual's circumstances.

Deprivation indices identify geographic areas of deprivation rather than identifying individual circumstances. This has been a criticism of them because they examine a heterogeneous group of people rather assessing individual circumstances. In urban areas, where the geographic area is relatively small, the social circumstances of the population are usually more homogenous. However, in rural areas there can be wide variation within enumeration districts with relatively deprived areas next to affluent

ones. A further criticism of deprivation indices based on the census is that they can only be updated every ten years; this has led to the development of scores which are not based on the census. However, the recent update of the Carstairs scores for Scotland has shown that there has not been a significant relative change in the socio-economic position of individual small areas (14) Despite these criticisms deprivation indices are extensively used for planning the allocation of resources to health boards by local, central and regional government.

2.2 Deprivation and Health in Glasgow

Deprivation has long been associated with poor health outcomes; both in self reported health measures as well as more subjective measures such as death rates. In the UK, between 1991-1995, men of social class 1 had a 9.5-year better life expectancy than men in social class V (the difference was 6.4 years in women). People of lower social class are more likely to die of diseases such as coronary artery disease and lung cancer (15). Scotland itself has higher mortality rates than England (16). However, differences in levels of deprivation between Scotland and England alone do not explain this difference. The gap in deprivation between Scotland and England actually narrowed between 1981 and 2001 but differences in mortality actually increased (16). While genetic differences between Scotland and England may be a possibility, it is unlikely that this entirely explains the mortality difference. It is more likely that this difference is due to Scottish people in an equivalent deprivation category to their English counterparts experiencing greater personal health risk.

In Scotland, a higher proportion of people suffer ill health compared with the rest of the UK. However, it appears that this poor health is not only a result of the health disadvantage from simply being deprived, it is also a result of the individual health behaviour of individuals. In Scotland, alcohol consumption is greater than the rest of the UK and smoking is more prevalent. In addition, there are lower levels of physical activity (16). The incidence of smoking is highest amongst the most deprived although paradoxically alcohol consumption is highest in the least deprived women (15). Therefore, levels of deprivation as well as the "Scottish Effect" have resulted in Scotland as a whole lagging behind England and Wales in terms of

improvements in health and mortality. This puts the deprived people of Scotland at even more disadvantage than the rest of the UK population in terms of survival.

Greater Glasgow contains eight of the ten most socio-economically deprived electoral wards in Scotland (17), as well as the nine of the ten worst off UK parliamentary constituencies, in terms of health (11). Compared with the rest of Scotland, Glasgow has the lowest life expectancy for both women and men. Incidence of ischaemic heart disease, smoking, hypertension, obesity and lung cancer, which are all associated with deprivation, are all above the national average (18). The levels of deprivation in Glasgow and the disparities between rich and poor within Glasgow itself (17) make it an ideal place to study the effects of deprivation on population health.

While it is not surprising that there should be differences in mortality in the diseases associated with socio-economic deprivation such as cardiovascular disease and lung cancer, what is surprising that disparities exist in mortality for cancers not associated with smoking, alcohol intake, obesity and lack of physical exercise. In fact, while the survival for many cancers has improved overall during the last 20 years, a gap in survival exists between affluent and deprived people and for some cancers it is actually widening. This gap persists even after correcting for widening differences in overall mortality between rich and poor (19). Delay in presentation or less effective access to healthcare may be responsible. Deprived patients tend to use NHS resources less, which may be due to the constraints of travel and childcare. In addition, affluent people may be more effective in communicating healthcare needs to their doctors.

2.3 Socio-economic differences in breast cancer incidence in Scotland

Like the rest of the Western world, the incidence of breast cancer in Scotland is highest in the more affluent socio-economic groups (fig 6)(12). While data on changes in incidence by deprivation in Scotland are not available, data from the West Midlands has shown that incidence is continuing to rise in affluent women while remaining relatively stable in less affluent women (20) (fig 7).

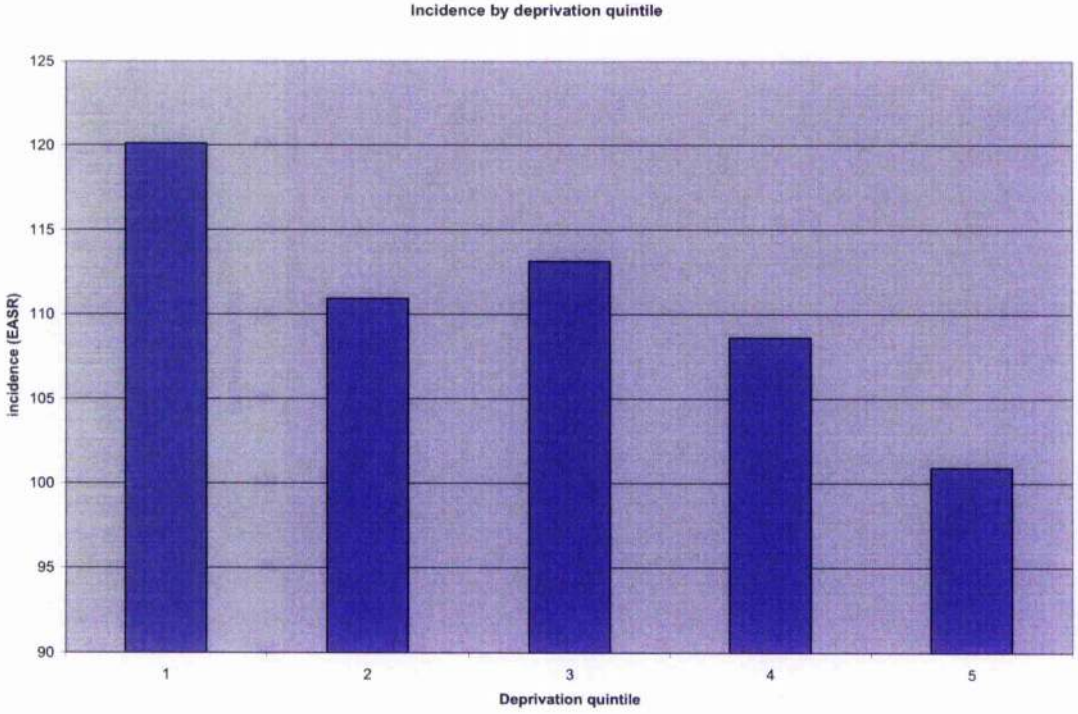


Fig 5: Differences in incidence for women diagnosed with breast cancer in Scotland by deprivation quintile using Carstairs scores between 1997-2001 (Data from ISD Scotland

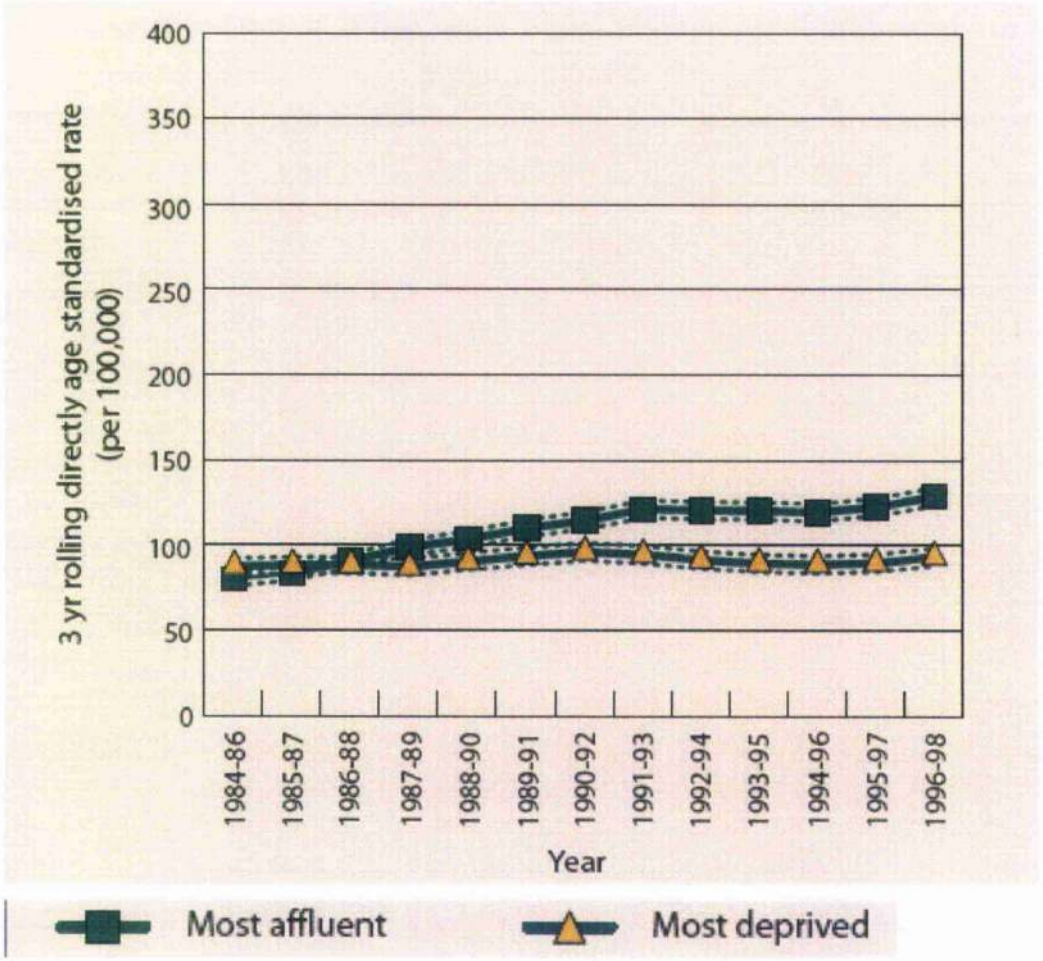


Fig 6: Variation in breast cancer incidence with deprivation in the period 1984 – 1998 for women in the West Midlands health region. Incidence measured by 3 year rolling directly age standardised breast cancer incidence rates in women of all ages in Townsend band 1 (most affluent) and 5 (most deprived)(20)

3 Reasons for socio-economic differences in incidence

3.1 Risk factors

The reasons why affluent women should have a higher incidence of breast cancer are not immediately obvious. It has been proposed that differences in their risk factors influence this dichotomy. Exposure to oestrogen is thought to increase the risk of breast cancer. The exact mechanism for this is unknown. Oestrodiol is thought to promote mitosis of breast epithelial cells thereby increasing the chance of dysplasia and eventually carcinogenesis (21). Reproductive factors which increase exposure to oestrogen are: nulliparity; late age at first pregnancy; early menarche; late menopause; and hormone replacement therapy (HRT) use (22). Each of these factors is affected by varying degrees by socioeconomic status and may contribute to differences in incidence of breast cancer between socioeconomic groups.

Pregnancy itself causes a transient increase in the risk of breast cancer due to the high levels of oestrogen during the pregnancy but only if a malignant transformation is already present in the breast. However, in the longer term the risk for breast cancer is increased in women who are nulliparous (23). In addition, an early age at first pregnancy reduces the future breast cancer risk. Affluent women are more likely to be nulliparous and be older at first pregnancy. Education and higher social class has been consistently linked with later age at first live birth and nulliparity (4). Affluent women have also been shown to have a shorter duration of breast feeding which could potentially increase their breast cancer risk because duration of breast feeding has also been shown to be protective against breast cancer (24).

Early menarche also results in an increased breast cancer risk. For every one year delay in the onset of menstruation there is a 5% decrease in breast cancer risk. This effect is most marked in premenopausal women (21). Between the 19th and 20th centuries there was a significant reduction in the age of menarche which was thought to reflect improved nutrition and environmental factors. However, in the last 20-30 years the reduction in age of menarche has been modest, at about 6 months (25). This probably explains why no socioeconomic difference has been demonstrated in

age at menarche between socioeconomic groups (4;25). Therefore, although age at menarche increases the risk of breast cancer it is unlikely to contribute to the socioeconomic differences in incidence.

Late menopause is associated with increased risk of breast cancer. The menopause causes a slow down in the increased breast cancer risk associated with aging (21). Socio-economic differences in the age of menopause have consistently been demonstrated regardless of the measure used. A recent study showed that material deprivation both during childhood and adulthood contributed to an early menopause (26). The reason for this difference is thought to be due to nutritional deficit in childhood leading to delayed growth and early menopause, while in adulthood behavioural factors such as obesity and smoking predominate. A later age at menopause in affluent women may also be contributing factors to socioeconomic differences in breast cancer risk.

HRT has recently been shown to increase risk of breast cancer. Use for 10 years and over accounts for an extra 19 cases of breast cancer per 1000 users of combined HRT (27). Use of HRT increases the length of time that breast tissue is exposed to oestrogen, thereby increasing the risk of breast cancer. HRT use has expanded rapidly since its introduction. However, affluent women are more likely to take HRT than deprived women (28). Therefore, differing patterns of HRT use between affluent and deprived women may account in part for socio-economic differences in incidence.

In addition to the reproductive factors which are thought to increase oestrogen exposure, obesity and dietary factors are thought to be linked to incidence of breast cancer. Postmenopausally, adipose tissue is the main source of endogenous oestrogen. It is thought that in obese patients there is excessive production of oestrogen which predisposes to breast cancer. In fact, obesity only predisposes to increased breast cancer risk postmenopausally (21). In premenopausal women, the amenorrhea associated with pubertal obesity appears to be relatively protective from breast cancer (29;30). In addition, high birth weight and childhood malnourishment are associated with an increased risk of premenopausal breast cancer (31).

It has been well documented that obesity is associated with material deprivation, both in adulthood and in childhood. The excess childhood obesity associated with deprivation might account for a lower incidence of premenopausal breast cancer in deprived socioeconomic groups. However, adulthood obesity in deprived socioeconomic groups contradicts the finding that affluent women have a higher incidence of postmenopausal breast cancer. This suggests that the relationship between socio-economic status and incidence of breast cancer is multifactoral and perhaps dietary factors are not as important as reproductive factors.

3.2 Breast Screening

Breast screening was first introduced in the UK in 1991. This resulted in a sharp rise in the incidence of breast cancer. The uptake of breast screening has progressively increased over time resulting in uptake rates of around 75% with a nationally agreed minimum standard of 70% (data from NHS breast Screening Programme). However, despite these high uptake rates social deprivation has a significant effect on the likelihood of attending for breast screening. Early studies carried out soon after the implementation of breast screening showed that there was a difference between socio-economic groups that was independent of distance from a screening centre (32;33). More recent studies have shown that this deprivation gap in attendance at breast screening persists despite efforts to improve attendance by targeting women from lower socio-economic groups (34;35).

The increased attendance at breast screening by more affluent women has resulted in a higher incidence of breast cancer in this group of women. However, the introduction of breast screening alone should cause an increase in the incidence of breast cancer in the women who attend for screening as the prevalent round is completed. It would then be expected that that incidence would remain at a constant rate but at a slightly higher level. Data from the West Midlands (fig 6) has shown that incidence in the screening age group is continuing to rise even after the prevalent round of screening has been completed. Moreover, this rise appears to be specific to affluent women while the incidence in deprived women is remaining relatively constant (20). This suggests that although breast screening affects incidence in the short term by identifying prevalent tumours, the long term effects are not so clear

cut. Breast screening appears to identify the slow growing tumours which would never have been clinically apparent. Affluent women are more likely to attend breast screening so this may contribute to the increased incidence of breast cancer in this group. However, what is unexpected is the continuing rise in incidence in affluent women, which suggests that the increased rate of incidence in affluent women must be due to factors other than screening, for example, aetiological factors.

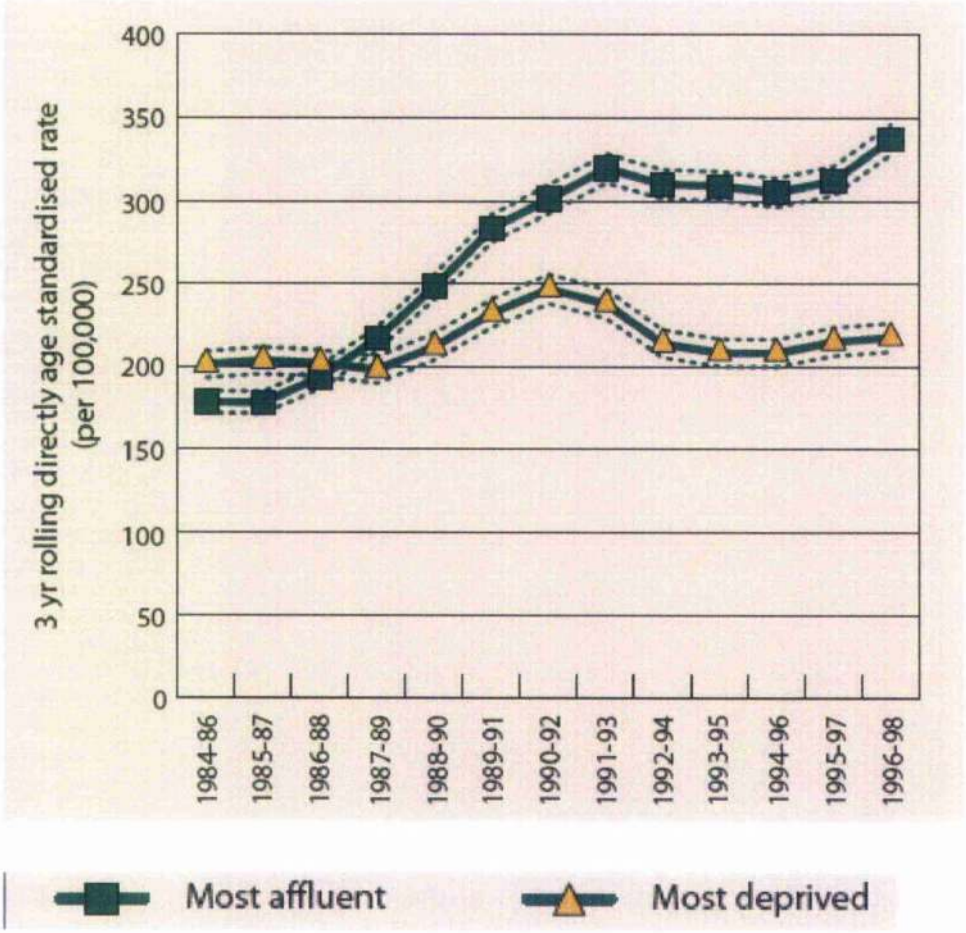


Fig 7: Variation in breast cancer incidence with deprivation in the period 1984 – 1998 . Incidence measured by 3 year rolling directly age standardised breast cancer incidence rates in women aged 50-64 in Townsend band 1 (most affluent) and 5 (most deprived) (20)

4 Socio-economic differences in breast cancer survival in Scotland

Despite the higher incidence in affluent women disparities in survival exist between affluent and deprived women in Scotland. In England and Wales survival is 5.8% better in affluent women (19). The deprivation gap in Scotland is largely similar at 6.6% (data from ISD Scotland – see fig. 8).

These differences between socio-economic groups exist regardless of the way socio-economic status is determined. Both area based measures (e.g. postcode) and individual based measures (e.g. social class) display the same relationship. It is difficult to assess individual socio-economic circumstances in large population based studies looking at trends in survival. This has necessitated the use of scores for geographic areas in order to assess survival trends over time. These tend to underestimate the actual size of the survival gap due to the assessment of heterogeneous groups of people. It was recently estimated that area based scores may underestimate the gap by up to 25 % (36). Therefore, the gap may be larger than estimated. In fact, socio-economic factors appear to override other demographic factors known to be associated with poor outcome from breast cancer. Studies from the USA have looked at racial disparities in breast cancer survival have shown that white women consistently do better compared with African-American women (37). However in the USA race is linked inextricably with socio-economic status and in fact, when data on race in corrected for socio-economic status there is no difference between ethnic groups (38).

Several reasons for these persistent survival differences have been proposed. It is thought that deprived women present with more advanced disease than affluent women (9;39;40). It has also been shown that deprived women are less likely to attend for breast screening (32-35). There has also been a suggestion that treatment for deprived women is different from that of affluent women (41). However, even correcting for these factors some of the survival difference cannot be accounted for and researchers have turned to other reasons to explain survival differences.

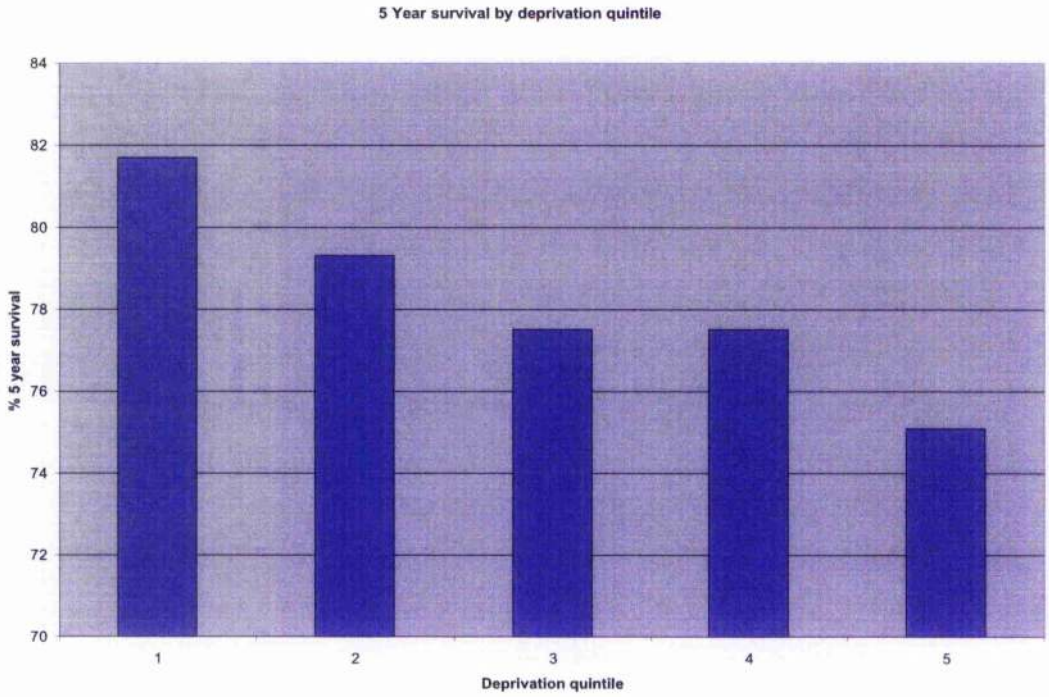


Fig 8: Differences in 5 year survival by deprivation quintile for women diagnosed with breast cancer in 1997-2001 (Data from ISD Scotland)

4.1 Pathological Factors

4.1.1 Pathology and Prognosis of Breast Cancer

Breast cancer is staged in several different ways. The TNM staging is in common use (see table 1) and can be grouped in to stage I to IV using the International Union Against Cancer (UICC) classification (see table 2). These different stages are important in determining prognosis.

The Nottingham Prognostic Index (NPI) can also be used to combine pathological factors to determine prognosis. It uses tumour size, lymph node stage (where stage 1 is no nodes involved, stage 2 is one to three nodes involved and stage 3 is four or more nodes involved) and histological grade (Bloom and Richardson I – III). These are combined to give the NPI:

$$NPI = 0.2 \times \text{size (cm)} + \text{lymph node stage} + \text{grade}$$

The NPI is then divided to give a score which determines prognosis(42) (see table 3)

Table 1: TNM Classification of breast tumours

Tis	Cancer in situ
T1	≤ 2 cm
T2	>2 cm - <5cm
T3	>5cm
T4a	Involvement of chest wall
T4b	Involvement of skin (including ulceration, direct infiltration, peau d'orange and satellite nodules
T4c	T4a and T4b together
T4d	Inflammatory cancer
N0	No regional node metastases
N1	Palpable mobile involved ipsilateral axillary nodes
N2	Fixed involved ipsilateral axillary nodes
N3	Ipsilateral internal mammary node involvement (rarely clinically detectable)
M0	No evidence of metastasis
M1	Distant metastasis (includes ipsilateral supraclavicular nodes

Table 2: Correlation of TNM classification with UICC stage (1987)

UICC stage	TNM Classification	% 5 year survival
I	T1, N0, M0	84
II	T1, N1, M0; T2, N0-1, M0	71
III	Any T, N2-3, M0; T3 any N, M0; T4, any N, M0	48
IV	Any T, any N, M1	18

Table 3: Correlation between NPI and 15 year survival

Prognostic Group	Index value	15 year survival
Good	≤ 3.4	80%
Moderate	>3.4 ≤ 5.4	42%
Poor	> 5.4	13%

Many attempts have been made to attribute breast cancer survival differences between rich and poor to tumour pathology and stage at presentation, but none of the findings have been consistent. Deprived women may present with later stage tumours (9;40;43), especially in the older age group (6). Despite these differences in pathology, none of these studies have managed to account for all of the survival difference. In contrast, two studies showed that although deprived women experience worse survival than more affluent women there is no evidence that they present with later stage disease(44;45).

These conflicting reports suggest that while some of the differences in survival may be due to different pathology, other factors must be involved. The fact that deprived women might present with later stage disease may be due to a delay in presentation either on the part of the patient or in that they are deprived of healthcare services. However, it has also been suggested that they may have higher grade disease (41) or hormone receptor negative disease (10) suggesting that deprived women are also developing more aggressive types of cancer.

4.2 Biological Factors

There is evidence that deprived women present with worse prognosis tumours in terms of histological grade (40;41) and ER status (10;46).

Tumour differentiation is scored and divided into three Bloom and Richardson grades. These grades predict survival, grade I having the best prognosis and grade III having the worst prognosis (47). Findings on the association between histological grade and deprivation have been inconsistent. Some of the larger studies that have identified survival differences between deprived and affluent women have not included an analysis on histological grade as information on grade as not available on

all patients (9;10;45;48). However, two studies which analysed pathological differences between deprived and affluent women identified that deprived women were more likely to have high grade disease (40;41). Because these studies did not include data on survival it is difficult to assess the contribution of histological grade at presentation to survival differences. Two studies based on patients in the West of Scotland showed that there was no difference in histological grade between deprivation groups (44;49). However, the proportion of patients in these studies who had information available on histological grade available were small which makes the findings less reliable.

Breast cancers can be divided into hormone sensitive and hormone insensitive tumours. The routinely measured hormone receptors are oestrogen and progesterone. Oestrogen receptor (ER) positivity determines response to endocrine therapy such as tamoxifen (an oestrogen antagonist) or the more recently available aromatase inhibitors. Treatment with tamoxifen reduces the chances of local recurrence by around 50% at 5 years and improves 5 year survival by around 25% in ER positive but not ER negative patients (50). ER positivity *per se* does not confer a survival advantage however it determines the response to tamoxifen which reduces the chance of recurrence and by extension improves mortality(51;52). Progesterone receptor positivity also gives a survival advantage(51) and although there is no therapeutic way of manipulating the progesterone receptor directly there is evidence that ER+/PR- tumours are more likely to be tamoxifen resistant than ER+/PR+ tumours (53).

The association between hormone receptor positive breast cancer and affluence is also contentious. Two studies have shown that low income and deprivation are associated with ER negative breast cancer (10;46). Thomson et al.(10) calculated that the difference in proportion of ER positive tumours between derived and affluent patients only accounted for 10% of the survival gap. Other studies have attempted to show that affluence is associated with hormone sensitive breast cancer but have failed to do so (41;44). There is therefore a suggestion that differences in hormone receptor status may have an influence on the survival difference but other factors are inevitably involved.

4.3 Treatment factors

4.3.1 Primary Care

Diagnostic delay in breast cancer results in reduced survival (54). The delay may be on the part of the patient in that they ignore breast symptoms or it may be that the way that primary care is delivered results in diagnostic delay (e.g. long waiting times for appointments with the general practitioner). It has not been shown consistently that deprived women wait longer before seeing their GP's with breast symptoms than affluent women. A meta-analysis of studies of reasons for diagnostic delay showed that the only factor consistently associated with delay in presentation to primary care was older age. The evidence for low income being associated with delay in presentation was only moderate (55).

In terms of provider delay there does not appear to be a socio-economic gradient. There is no difference in waiting times for referral between affluent and deprived women. In fact, following diagnosis, deprived women appear to consult their general practitioners more frequently than affluent women (56). Therefore, delivery of healthcare at the primary level does not appear to be a factor.

4.3.2 Secondary Care

Surgery for breast cancer

The mainstay of treatment for breast cancer is surgery, either with breast conservation surgery or mastectomy with axillary staging. If a woman has a mastectomy they also have the option of immediate or delayed reconstruction. Until the early 70's, the modified radical mastectomy, as described by Halsted (57), was the only surgical treatment for invasive breast cancer. Over the years since it was first described there were a few minor modifications involving excision of the internal mammary nodes (58) or preservation of the pectoral muscles (59). Changes were made to the extent of lymph node dissection but essentially the extent of surgery remained largely unchanged.

Breast conservation surgery with adjuvant radiotherapy was compared with mastectomy in two randomised controlled trials in the 70's. Five year follow up suggested no survival difference between the two treatment modalities (60;61). Comparison of outcome at 20 years again confirmed that there was no survival difference between the two procedures. The only disadvantage was that in conserving the breast there was a higher risk of local recurrence but this did not affect survival (62;63). Several other randomized controlled trials confirmed these findings (64-66). These trials were limited to patients with small tumours (less than 5 cm) and four relative contraindications to breast conservation surgery have since been identified. (1) 1st or 2nd trimester of pregnancy (2) history of previous therapeutic irradiation of the breast (3) multifocal disease (4) extensive microcalcifications seen on mammography. Other relative contraindications were a large tumour in a small breast that would result in an acceptable cosmetic outcome(67).

Despite the extensive evidence that conservation is as effective as mastectomy and the recommendation of conservation for early stage breast cancer, uptake of conservation surgery has not been uniform. Based on figures from the United States, it has been estimated that 10% of tumours smaller than 2cm and 30% of tumours between 2cm and 5cm require mastectomy due to a medical contraindication (68). Despite the guidelines, studies have shown rates of conservation to be widely varied. Some studies have reported rates as low as 15% (69) while others have reported rates as high as 85% (70). In addition, data published on mastectomy rate from the recent ATAC trial showed wide geographical variation in mastectomy rate of between 20 and 97% (71).

The reasons behind these wide variations in mastectomy rate are not entirely clear. The international differences suggest that some of the reasons might be cultural but variation is also seen within countries. It may be the way that treatment options are presented to the patients, they may be presented in a biased manner or the option of conservation surgery is not presented at all (69). Older, male surgeons as well as surgeons with a smaller caseload (39) are also less likely to recommend conservation surgery . In addition, race and socio-economic status also appear to be important in determining surgical management (72) . The surgeons recommendation has been

shown to be of primary importance in determining surgical management (73;74) so physician factors are probably more important than demographic factors. Although if this is the case, there might be the uncomfortable implication that surgeons are in some way be responsible for the demographic differences because they treat women from different backgrounds differently.

Differences in surgical management between socio-economic groups

Many studies from the USA have shown that women of lower socio-economic status are more likely to have a mastectomy, independent of tumour characteristics (38;72;75-77). Mastectomy is a slightly cheaper surgical option because it does not include the added expense of adjuvant radiotherapy. However, it is difficult to extrapolate these findings to the UK where healthcare is not paid for directly by the patient. Findings in the UK have been less consistent. There have been two studies showed that deprived women are more likely to have a mastectomy (10;41) but in both of these this was not the primary outcome that was being examined in the studies. A study from Denmark, where healthcare is state provided, also found that there was a difference between affluent and deprived women in surgical management (78). On the other hand a study of women in Glasgow showed that there was in fact no difference (49). It appears therefore that, while some of the reason that deprived women should tend to have more mastectomies, independent of tumour stage, is related to the actual monetary cost, there must be other reasons as well.

In studies looking at factors involved in choosing surgical management, the excess cost of travelling to and from a radiotherapy centre and the cost of childcare have been identified as important in persuading women to have a mastectomy (79;80). Both of these studies were conducted in the USA and the cost of healthcare being largely borne by the patients may be a confounding factor in these two studies. The additional finding in a study by Morrow et al (81) that income also influences use of reconstruction suggests that it is the financial cost which is most important. Whether financial factors influence choice of surgery in the UK to such an extent is not clear. However, if the recommendations of the surgeon supersede these reasons (72;73), perhaps the way treatment options are presented to the patient are not entirely impartial.

It is important to not only understand why there is such wide variation in mastectomy rate but also why certain groups of patients are more likely to have a mastectomy than others. Initially, it was thought that having a mastectomy did not cause psychological morbidity and early studies showed no difference between women treated with the two types of surgery (82). It was thought that the lack of difference was due to patients' concern about recurrence using the less radical technique. However, a more recent prospective study with 5 year follow up has shown that conservation surgery is associated with better body image and better function in terms of work and hobbies. This difference was noted across the age groups. Quality of life scores improved over time for the conservation surgery patients but not the mastectomy patients (83). This implies that it is important to ensure that conservation surgery is offered to anyone who is eligible regardless of age or other demographic factors.

Despite the psychological co-morbidity of having a mastectomy, having a choice between conservation surgery and mastectomy actually results in lower levels of anxiety and depression (84). It has been shown that deprived women have been shown to adopt a passive role in decision making for breast cancer (85). Whether this passive role is due to patient choice or a more "paternalistic" attitude on the part of the surgeon where they are not actually offered a choice of surgery is unclear. When asked, patients, regardless of socio-economic status, tend to prefer a more collaborative role in decision making where their opinions and preferences are taken into consideration by the surgeon (86). In addition, a recent study in Glasgow on the information given to women with breast cancer showed that deprived women received less information than their more affluent counterparts and had higher anxiety scores when tested several years following completion of treatment (87). Thus, if deprived women are having more mastectomies because they are being denied the choice of surgery rather than due to clinical need, they may well have excessive psychological co-morbidity not only due to the type of surgery but also the lack of choice. It also appears that it is the surgeons themselves may be contributing to this psychological co-morbidity, particularly in deprived women. While psychological co-morbidity does not translate into survival differences, it has implications for quality of life.

4.3.3 Breast Screening

Socio-economic inequalities in breast cancer exist not only in treatment but also in uptake of breast screening. It is well known that deprived women are less likely to attend breast screening(33). In Greater Glasgow the uptake for breast screening in the period 1999-2000 – 2001-2003 was 67% compared with a Scottish average of 75% (data from ISD Scotland). The Glasgow uptake rate falls short of the national standard of more than 70 % set by the National Health Service Breast Screening Programme (NHSBSP). Part of this deficit is probably a reflection of the high levels of deprivation in Glasgow. For Scotland as a whole the uptake in dep cat 7 is below 60% compared with just over 80% in dep cat 1(data from ISD Scotland – see fig 9).

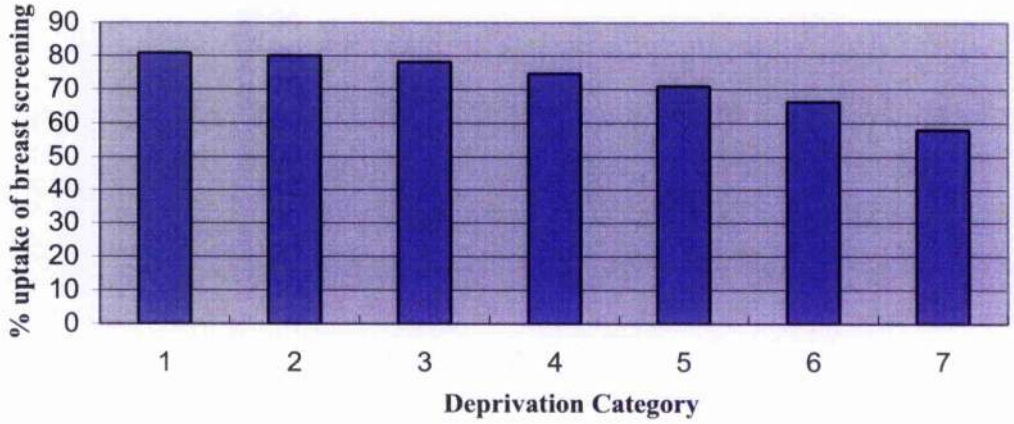


Fig 9: Uptake of breast screening in Scotland by deprivation category (data from ISD Scotland)

It is not clear whether these differences in uptake of screening translate into survival differences between rich and poor and whether they have exaggerated the previously described survival differences. Screen detected tumours have a better prognosis at diagnosis than those that present symptomatically because they tend to be smaller (88) and have a better prognosis (33). This improved prognosis is seen among all

levels of deprivation, however, with the different uptake of screening between more and less well off women, it might be expected that breast screening would compound the existing survival differences. In fact, a study of the Northern and Yorkshire breast cancer registry showed that there were strong gradients of stage and grade between socio-economic groups and this difference was particularly marked in the breast screening age group (40). From this study it appears that breast screening may have actually caused a widening of the deprivation gap, but without any data on survival it is difficult to draw any firm conclusions from this.

There is some limited data available on trends in mortality between socio-economic groups since the introduction of breast screening but it gives conflicting results. A recent study based on patients in Glasgow looked at the pathological and survival differences between a group of patients diagnosed in a year prior to the start of the NHSBSP and following the institution of the NHSBSP. They noted a difference in 8 year survival between the most and the least affluent of about 10% in both the pre- and post- breast screening cohorts of patients, despite an overall increase in survival of about 10% (89). This suggests that breast screening has improved outcome for all women rather than being selectively beneficial for affluent women. Data from the West Midlands has suggested that the deprivation gap is actually closing between the most and least affluent. They found that the difference in 5 year survival between most and least affluent women was 12% for women diagnosed between 1984 and 1988 but the gap had narrowed to 8% for women diagnosed in 1994-1998 (20). It is therefore difficult to know whether the breast screening programme is contributing to or improving disparities in outcome. Clearly, with this lack of data on survival differences in the post-breast screening era, it is important to re-examine what impact breast screening has had.

4.3.4 Health Board

Geographical variation also appears to contribute to inequalities in breast cancer outcome. Several studies have shown that geographical variation exists between different health boards, in Scotland, (90) or health authorities, in England and Wales, (48). Health authorities with higher levels of deprivation appear to have worse outcomes from breast cancer but not all of the difference is explained by deprivation alone. This suggests that perhaps it is not deprivation alone that is resulting in poorer

outcome for women from the under-performing health boards/ authorities, but the way that cancer services are provided and delivered. If there is variation between health authorities/ boards this might compound socio-economic inequalities.

The surgeons operating within each health authority may also be contributing to geographical differences. Previously, it has been shown that the degree of specialisation and the caseload of the operating surgeon influence breast cancer survival (91;92). More recent data however, has shown that the specialisation of the surgeon does not make any difference to 10 year survival (89) , so the surgeons alone are not causing the differences between health boards. While deprivation does play a role in geographical variation in 10-year survival, there are clearly other factors in health care delivery, such as operating surgeon and availability of adjuvant therapy, that also play a role. With the introduction of multidisciplinary team working and more uniform prescribing of adjuvant therapy some of these geographic differences and should be removed and perhaps by extension some of the differences between socio-economic groups.

5. The Systemic Inflammatory Response, Deprivation and Breast Cancer

Clearly there are many factors that might contribute to differences in outcome between socio-economic groups. These centre around treatment factors and pathological factors. However, the way that the host responds to the tumour may also have an effect on outcome. Recently, the presence and magnitude of a systemic inflammatory response to cancer has been identified as prognostic in patients with malignancy. Recent work has suggested that the magnitude of the response varies with the type of tumour and can predict recurrence, cancer specific and overall survival, independent of clinical stage (93). In addition, recent studies have also shown that people from deprived socioeconomic groups have a raised "background" systemic inflammatory response (94;95) and it has also been suggested that they may have an elevated systemic inflammatory response to cancer which may account for their poorer cancer survival (96).

The Systemic Inflammatory Response

The systemic inflammatory response occurs in the presence of tissue injury. For example, it occurs in response to infection, trauma, surgery, burns, tissue infarction, various immunologically mediated and crystal-induced inflammatory conditions as well as cancer. Following tissue injury there is a release of pro-inflammatory cytokines, which then induce an acute phase protein response. These are predominantly IL-6, IL-1β and TNF-α, IFNγ, TGFβ and IL-8. These are released from a variety of cells but macrophages and monocytes are the most important, while Il-6 is the most important cytokine in inducing the production of the acute phase proteins by the hepatocytes of the liver. IL-6 was initially identified in B-cells but it is also produced by T cells, endothelial cells, macrophages and epithelial cells. However, the cytokines do not simply act as a cascade to induce the production of the acute phase proteins they also act as a network. Thus there is a complex interaction between the pro-inflammatory cytokines, with Il-6 as the most important, which result in the acute phase protein response (97).

The acute phase response is characterised by the release of the acute phase proteins, the most marked response coming from C-reactive protein and Serum amyloid A. These have therefore become the prototypical serum markers of the acute phase response. C-reactive protein has the advantage over serum amyloid A in that there are defined standards on how to measure it, it is a more stable molecule, has no diurnal rhythm and is not altered in the fasted and fed states (97). Moreover, CRP testing is cheap and widely available. It is therefore C-reactive protein which is used in routine clinical practice as a marker for the systemic inflammatory response.

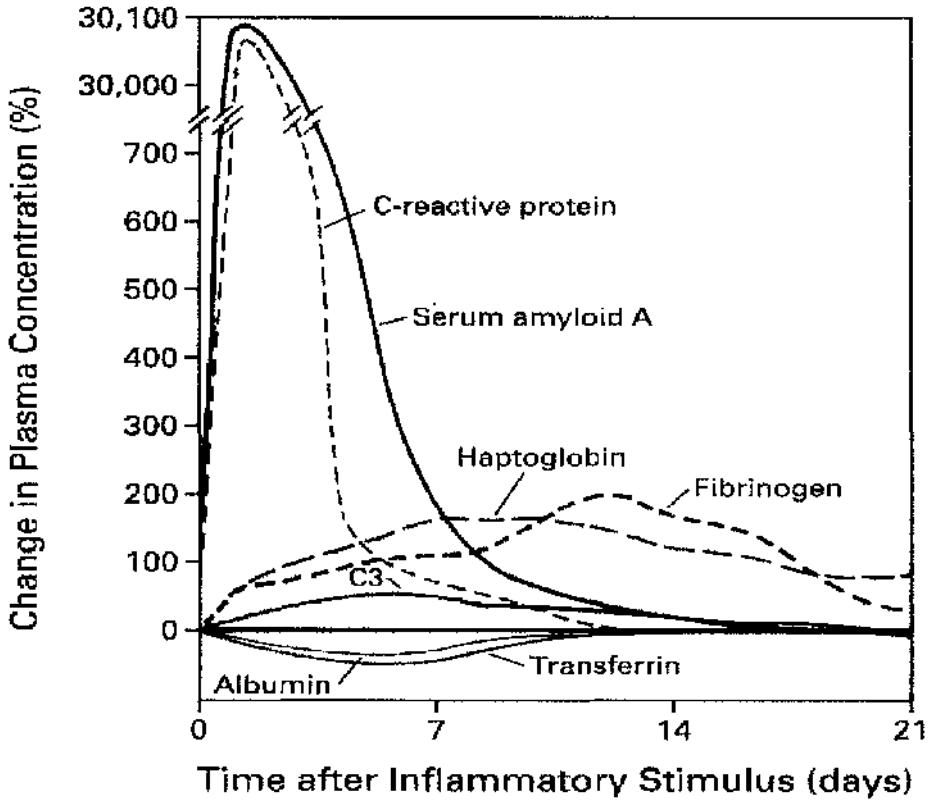


Fig 10: Changes in plasma concentration of the acute phase protein in response to an inflammatory stimulus (97)

The signalling pathway in the hepatocytes which induces the production of C-reactive protein mRNA involves IL-6 binding to its receptor (IL-6Rα). IL-6Rα then forms a complex with the signal transduction molecule gp 130. This then further activates and phosphorylates the JAK kinases, which in turn activate C/EBPβ and STAT 3, resulting in the production of C-reactive protein mRNA. Levels of IL-6 in the serum and levels of C-reactive protein are correlated with one another both in cancer patients (98) and in patients with cardiovascular disease (99).

C-reactive protein was first discovered in the serum of patients with pneumococcal pneumonia. It was so named because it reacted with the pneumococcal C polysaccharide (97). Despite the fact that it was discovered almost 80 years ago its exact functions are not well known. The acute phase reactants are thought to limit tissue damage. C-reactive protein has been shown to have several functions *in vivo*. It acts as a scavenger molecule opsonising bacteria, fungi and parasites. It also binds neutrophils and macrophages and can activate the classical complement pathway (100). While a systemic inflammatory response is advantageous when there is tissue injury, in patients with cancer, a systemic inflammatory response can be detrimental.

The Systemic Inflammatory Response and Cancer

The systemic inflammatory response appears to be important in the development and progression of neoplasia and appears to modulate the hypermetabolism, cachexia and malnutrition associated with cancer. The acute phase response results in the reprioritisation of hepatic protein synthesis to produce the acute phase reactants. This in turn results in decreased production of the essential amino acids and the breakdown of skeletal muscle. A similar response is also seen in infection and trauma. While in the presence of infection the presence of this response is beneficial and may aid tissue repair, blood clotting, prevent ongoing tissue damage and destroy infective organisms, its role in cancer is not known. In patients with cancer it results in increased energy expenditure and accelerated weight loss and its presence is associated with a poor prognosis (101).

IL-6 has been implicated as important in the induction of the acute phase response to cancer. In a variety of cancers IL-6 is released from both the cancer cells themselves and the neighbouring tissues (98). The effects of IL-6 itself on tumour growth appear to be variable. It exhibits both autocrine and paracrine effects on tumour cells. *In vitro* studies have shown that it can be inhibitory or it may promote tumour growth. Results from *in vivo* models have been equally conflicting and the result appears to depend on the model used (102). An elevated serum IL-6 has been demonstrated in patients with a variety of solid tumours (98;103-106) although its ability to predict prognosis independent of pathological variables has been inconsistent (104;106-108).

IL-6 appears to be related to the nutritional status of the patient with advanced cancer. In animal models administration of IL-6 results in an acute phase response associated with anorexia, weight loss and increased protein and fat breakdown (101). However in humans an elevated IL-6 has only been shown to associated with an acute phase protein response and malnutrition in patients with lung and colorectal cancer as well as lymphoma (101;109). A significant amount of IL-6 is also produced peripherally in the tissues which may not be measured by serum estimation (101). Thus although IL-6 is clearly important in the induction of the acute phase protein response to cancer it probably does not act independently but acts as part of a network of cytokines (which includes Il-1β and TNF-α, IFNγ, TGFβ and Il-8). Measurement of IL-6 in the serum does not correlate well with prognosis or malnutrition associated with cancer.

C-reactive protein is elevated over 1000 fold in the acute phase protein reaction. An elevation in the concentration of C-reactive protein is produced in response to increased elaboration of IL-6 either by inflammatory cells or tumour cells. In patients with colorectal, pancreatic, gastric and lung cancer a raised C-reactive protein has been shown to be associated with a reduced cancer specific and non-cancer specific survival, which is independent of stage at presentation (93). While the end product of a raised systemic inflammatory response is the cachexia and malnutrition associated with cancer, the reason why some tumours should induce an enhanced inflammatory response more than others is not clear.

The tumour cells themselves may be capable of producing their own cytokines which may promote tumour growth and proliferation. In turn these cytokines induce the systemic inflammatory response and its *sequelae*, making this a tumour derived response. Alternatively, the production of cytokines may come from the injured tissues making the systemic inflammatory response a host derived response. In fact, in colorectal cancer a poor lymphocytic infiltrate is associated with a poor prognosis and an enhanced systemic inflammatory response (110), suggesting that the tumours themselves produce their own cytokines rather than the surrounding tissues. While in renal carcinoma greater lymphocytic response is associated with a raised systemic

inflammatory response and a poor prognosis (111) , suggesting that it is the surrounding tissues that produce the inflammatory response.

The Systemic Inflammatory Response and Breast Cancer

Breast cancer does not tend to be associated with nutritional depletion and weight loss, except in its latter stages, in the same way as pancreatic, gastro-oesophageal or colorectal cancer. Thus the systemic inflammatory response in breast cancer has not been as well characterised as in the more "inflammatory" tumours and results have been less consistent.

For this same reason the inflammatory response has been studied in patients with metastatic breast cancer more than those with primary disease. Serum IL-6 has been shown to be raised in patients with breast cancer more than in healthy controls and it is also raised in patients with metastatic disease more than those with only loco-regional disease (112). A raised serum IL-6 predicts poor prognosis (102;113-115) in metastatic breast cancer as well as response to chemotherapy (115). In addition it also predicts the number of sites of metastases (102) suggesting that the magnitude of the host response is associated with the extent of disease. What is not known is if a raised IL-6 predicts outcome in patients with primary breast cancer.

The role of the systemic inflammatory response, as reflected in a raised CRP has not been fully elucidated in breast cancer. A raised CRP has been demonstrated in patients with locally invasive and ulcerating breast tumours but not in patients with earlier stage disease. In this study the presence of a systemic inflammatory response did not predict survival (116). Patients with metastatic disease have been included in studies of a heterogeneous group of patients with solid tumours which showed that the systemic inflammatory response predicted survival (93;117). However, only one study has assessed the relationship of the systemic inflammatory response to survival in breast cancer. This study looked at patients with metastatic disease and showed that serum CRP combined with serum albumin predicted survival (118). What is not known is how the systemic inflammatory response relates to survival in primary disease.

The systemic inflammatory response and deprivation

There is some suggestion that people from lower socio-economic groups have a greater systemic inflammatory response to cancer compared with the more affluent. In healthy subjects, higher levels of socio-economic deprivation are associated with an enhanced inflammatory response. For example, measurement of background levels of C-reactive protein in randomly selected male subjects has shown that socio-economic deprivation is related to a higher level of C-reactive protein, after adjusting for smoking, waist-to-hip ratio and prevalence of other diseases(94;95). C-reactive protein is known to be raised in a number of disease states, particularly in cardio-vascular disease, obesity and smoking (119). Both of these have a higher incidence in people of lower socio-economic status, and may account for why they have a raised C-reactive protein compared with people of higher socio-economic status.

There is some evidence in colorectal cancer that a difference in the magnitude of inflammatory response might account for survival differences between socio-economic groups. Patients with colorectal cancer who had a raised preoperative CRP were shown to have a worse cancer specific and non-cancer specific survival. In addition deprived patients had a worse non-cancer specific survival (96). While there was no direct link between a raised CRP and deprivation in this study, a raised CRP in deprived patients appeared to account for the effect of deprivation on cancer survival.

Whether this relationship exists in breast cancer is not clear. A recent study has shown that deprived women with breast cancer have a raised pre-operative C-reactive protein compared to more affluent women. This rise was not related to tumour stage at presentation (120). This study used standard laboratory C-reactive protein with a sensitivity of >6mg/l. Data was not available on survival so it is not clear whether this raised inflammatory response was related to survival. It does however pose the question that perhaps the systemic inflammatory response might contribute to survival differences observed between affluent and deprived women.

6. Summary

A paradox appears to exist in breast cancer survival and incidence. While affluent women are more likely to develop breast cancer, deprived women tend to die of the disease. These findings have not been consistent in all studies but it does appear to be a general trend. Several factors have been suggested for the reason behind the deprivation gap: tumour pathology, hormone sensitivity, treatment both in primary and secondary care, access to breast screening and the way that breast cancer services are provided. A further more novel reason for survival differences may be in the nature of the systemic inflammatory response to breast cancer by deprived and affluent women. This has never been demonstrated in breast cancer but has been suggested in colorectal cancer.

Many of the studies examining the deprivation gap were carried out prior to the introduction of breast screening. Breast screening has increased the incidence of breast cancer overall but appears to have increased it more in affluent women. This may have influenced the presence and magnitude of the deprivation gap but there have been few studies examining this.

Aims

The thesis aims to examine, in a population of patients with breast cancer in the post breast screening era, if a deprivation gap in survival persists. Furthermore, it will assess what potential reasons may underlie a survival difference, if it exists.

The first chapter will establish whether the deprivation gap still exists in Glasgow in terms of survival from breast cancer. Using the Greater Glasgow Breast Cancer Audit database, which has over 5 year follow up for patients undergoing surgery for primary operable breast cancer, survival will be analysed to see if deprivation has any influence on it. Other factors such as pathology and treatment will also be examined to see if they affect outcome.

Although there is no difference in survival between patients undergoing mastectomy compared with conservation surgery, it is accepted that overall breast conservation surgery is underutilised. One of the factors that may be contributing to this is deprivation. The second chapter will assess if the mastectomy rate in Glasgow is higher than reported in the literature and to what extent deprivation contributes to this.

The risk factors associated with ER positive breast cancer are known to be more prevalent in affluent women and ER positive breast cancer carries a better prognosis. Over time the risk factors associated with ER positive breast cancer have increased but more rapidly in affluent women. The third chapter will assess if there has been an increase in ER positive breast cancer over time and whether this increase has been more pronounced in affluent women, which might account for some of the survival differences.

Finally the host systemic inflammatory response will be examined as a potential contributing factor to survival differences. Firstly, if the presence of the systemic inflammatory response predicts survival in breast cancer and also whether there is a difference in magnitude between affluent and deprived women.

Chapter 1

Does the deprivation gap in breast cancer still exist?

Introduction

It has long been established that there is a deprivation gap in survival from breast cancer (5;6;10;19). Evidence that women from deprived areas present with more advanced disease has been inconsistent (40;44;45;49). The uptake of breast screening is certainly worse in women from more deprived areas (32-35), while this may have affected the incidence in affluent women, it is not clear how this has impacted on survival differences.

There also remains persistent geographical variation in survival (8;48;90), although a recent study in Scotland has suggested that this variation has improved since the introduction of breast screening and multi-disciplinary team working (89). Geographical variation may exacerbate socio-economic differences if the areas concerned are homogenous in terms of deprivation. The reason that geographical variation exists may be due to differences in socio-economic status of the population or, more concerning for clinicians, it may be that there is inequality in the provision and delivery of healthcare. There has also been a suggestion that surgery for breast cancer has not been performed adequately in the past and there is a survival advantage to being treated in a specialist breast unit (91;92;121;122).

The "deprivation effect" has been described extensively in previous studies in groups of women before the establishment of breast screening. However, with the establishment of breast screening, patients were treated in dedicated breast units and their treatment was determined by the multidisciplinary teams. The benefit of this is that healthcare provision should become more equal between socio-economic groups and between geographical areas and should therefore limit the deprivation gap. With this in mind, the Greater Glasgow Breast Cancer audit was set up. A multidisciplinary cancer network of specialist breast units was established in Greater

Glasgow. This network identified minimum standards of treatment in an attempt to standardise it and also to try to redress the balance between the treatment that women from different areas were receiving. Minimum standards were identified in surgical treatment, pathological assessment of the resected tumour and post-operative adjuvant therapy. All patients were managed by specialist breast teams in specialist clinics all under the umbrella of a managed clinical network. All data on patients was collected prospectively and held by the Greater Glasgow Health Board. Results were intermittently audited to ensure standards were being maintained and the breast units were being compliant.

The establishment of managed clinical networks (MCN) was championed by the Calman Hine report (123) which was published around the time that the Glasgow Managed clinical network was established. However, the Glasgow MCN was the first example of an MCN in Scotland.

As part of the follow up to the establishment of the MCN, all patients were followed up by case note review to assess outcome and to see if it had improved overall, but also to see if standardised management by specialist breast teams removed the variation associated with geography; treatment by specialist versus non-specialist surgeons; and socio-economic deprivation.

The aim of this chapter is to examine whether there is variation in survival associated with deprivation in patients who were entered onto the database between 1995 and 1998; and secondly what factors if any are associated with differences in outcome.

Methods

Standards audited

The standards established by the Glasgow Managed clinical network were divided into diagnostic standards, surgical treatment standards, pathology standards and standards in adjuvant therapy.

Diagnosis

All patients should be treated by specialist breast surgeons in the context of a specialist breast clinic

Surgical Management

Patients should have adequate clearance of their tumour

All patients should have full axillary staging

Pathology

Tumour size, type and grade should be assessed

All resected nodes should be examined for metastasis

Oestrogen receptor status should be measured using immunohistochemistry, with greater than 10% positive staining as a cut off for ER positivity

Adjuvant therapy

All node positive women should be considered for chemotherapy (cyclophosphamide, methotrexate and fluorouracil (CMF) or anthracyline based in the context of a clinical trial in this time period)

High risk, node negative tumours should also be considered for chemotherapy (i.e. ER negative tumours that were high grade or had lymphovascular invasion)

Radiotherapy should be given to all women having conservation surgery and to those high risk patients who had a mastectomy (large, node positive tumours)

All ER positive patients should be offered hormonal therapy (tamoxifen for the majority of patients)

Data on the above standards were collected prospectively on women with primary operable, breast cancer between October 1995 and December 2001. Women were treated at 5 different Glasgow hospitals (Glasgow Royal Infirmary, Western Infirmary Glasgow, Victoria Infirmary Glasgow, Southern General Hospital, Stobhill Hospital). Each is staffed by specialist surgical teams and treatment is determined in

the context of a multidisciplinary team meeting. The compliance of the audit was assessed at intervals to check the standards were being maintained.

Data Collection

The period studied for this study was 1995-1998. During the study period, 1988 patients were diagnosed with primary operable breast cancer and received surgical resection of their disease. Surgical management was divided into "conservation surgery," (lumpectomy with axillary staging) and "mastectomy" (mastectomy with axillary staging) or limited resection (lumpectomy or mastectomy only).

Details of tumour pathology were collected, including histological grade, size, axillary node status and oestrogen receptor status. ER status was determined using immunohistochemistry, with greater than 10% staining considered positive. Tumour size, grade and lymph node status were combined and expressed as the Nottingham prognostic index. Nottingham prognostic index was then divided into good prognosis (NPI < 3.4), intermediate prognosis (NPI 3.41 – 5.4), and poor prognosis (NPI > 5.4)

Patient demographics collected were: age and deprivation category and year of diagnosis. Deprivation was determined using the method of Carstairs and Morris (14). Postcode sectors are analysed for the prevalence of various census variables associated with socio-economic status, these are: ownership of a car, proportion of people in social classes IV and V, overcrowding and male unemployment. Postcode sectors are then scored and categorised into seven deprivation categories. For the purposes of this study, categories 1 and 2 were combined to "affluent"; 3, 4 and 5 were combined to "intermediate"; and 6 and 7 were combined to "deprived".

Follow up

Patients were all followed up at 5 years. Initially a search of the death registry was made for patients who were deceased since diagnosis. An additional search was made for cause of death. The case notes were then reviewed for all patients over the course of a year. Those patients who had not been reviewed in the breast clinic post-operatively or case notes were not available, were followed up by contacting their GP to check whether they were still alive.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 9 (SPSS, Chicago, IL). Age, tumour size, histological grade, nodal status, oestrogen receptor (ER) status, year of surgery, surgical management and method of diagnosis and were individually examined for their association with deprivation category using χ^2 tests of association.

Kaplan Meier technique was used to give a crude measure of overall survival from time of diagnosis to time of death and the relationship between deprivation and survival was obtained using a Log Rank test. Univariate survival analysis was performed using a Cox regression model to identify if there was a relationship between deprivation and survival. A Cox regression model was also used to assess the relationship between age at diagnosis, tumour size, tumour grade, nodal status, ER status, year of surgery, type of surgery and method of diagnosis. A multivariate Cox regression model was then constructed to identify which factors were independent predictors of survival.

This was a retrospective audit using data previously collected so ethical permission was not required.

Results

In total 1988 patients were treated for breast cancer in the study period. 243 patients were excluded who had DCIS and no invasive breast cancer. In addition, 10 patients who had no deprivation category recorded were excluded. Case notes could not be obtained for 13 patients and these patients were also excluded. This left 1717 patients diagnosed between 1995 and 1998 with data available for analysis.

The majority of patients were over 50, with the largest proportion of patients (32%) in the age group 55-64. Most patients were in the intermediate deprivation category (47.6%) with 18% of patients in the most affluent group and 34.4 % of patients in the least affluent group. There was a roughly even proportion of tumours treated in each year of the audit although there was a smaller number in the first year because the audit did not start until October 1995.

More patients had a mastectomy (58%) than had conservation surgery (40.1%), while only 1.9% had a resection but no treatment of their axilla. The majority of patients had symptomatic tumours (66.9%) while 32.0 % had screen detected cancers.

Most patients (63.2%) had small tumours (<2 cm), although 34.1 % had tumours between 2 and 5 cm, with only 2.5 % having tumours greater than 5 cm. The majority, 48%, had intermediate grade tumours, 22 % had low grade tumours and 29.1% had high grade tumours. The majority of tumours were node negative (58.4%) and ER positive (73%).

Table 3: Clinicopathological features of participants

	Number of patients	percentage
Age		
<25	2	0.1
25-34	27	1.6
35-44	189	11.0
45-54	434	25.3
55-64	550	32.0
65-74	345	20.1
75+	170	9.9
Deprivation category		
Affluent	309	18.0
Intermediate	818	47.6
Least affluent	590	34.4
Year of surgery		
1995	134	7.8
1996	531	30.9
1997	602	35.1
1998	450	26.2
Surgery		
Conservation surgery	689	40.1
Mastectomy	995	58.0
Limited resection	33	1.9
Mode of presentation		
Symptomatic	1149	66.9
Screen detected	548	32.0
*Other**	*20*	*1.1*
Tumour size		
<2 cm	1086	63.2
2 cm - 5 cm	585	34.1
>5 cm	43	2.5
Unknown	*3*	*0.2*
Grade		
I	388	22.6
II	824	48.0
III	500	29.1
Unknown	*5*	*0.3*
Lymph node status		
Negative	1002	58.4
1-3	446	26.0
≥4	232	13.5
Unknown	*37*	*2.2*
ER status		
Positive	1254	73.0
Negative	421	24.6
Unknown	*42*	*2.4*

* *e.g. family history screening*

In general, deprivation was associated with worse tumour pathology (see table 4 below). Deprived patients had significantly larger tumours than the affluent or intermediate group (χ^2: p=0.003). There was no significant difference in tumour grade between the deprivation categories (χ^2: p=0.224). However, there were significantly fewer node negative tumours in the least affluent group although this relationship was of borderline significance (χ^2: p=0.045). When tumour factors were combined and expressed as the NPI, deprivation was strongly associated with worse NPI (p <0.001). There was no significant relationship between deprivation and ER status ((χ^2: p = 0.744).

Deprived patients were more likely to have a mastectomy than the affluent or intermediate groups (63.1% vs. 57.9 and 54.3 % respectively) (χ^2: p=0.002). Intermediate deprivation patients were most likely to be diagnosed at breast screening compared with affluent and deprived patients (37.5% vs. 26.5 % and 28.1% respectively (p <0.001).

Table 4: Association of deprivation with pathology and treatment

Variable	Affluent (%) N=309 (18.0)	Intermediate (%) N=818 (47.6)	Deprived(%) N=590 (34.4)	χ^2	P
Tumour size					
<2 cm	209 (67.6)	541 (66.2)	336 (57.1)	15.80	0.003*
2-5 cm	95 (30.7)	257 (31.5)	233 (39.6)		
>5 cm	5 (1.6)	19 (2.3)	19 (3.2)		
Grade					
I	78 (25.2)	178 (21.8)	132 (22.4)	8.201	0.224
II	136 (44.0)	416 (50.9)	272 (46.1)		
III	93 (30.1)	222 (27.1)	185 (31.4)		
Not Known	*2 (0.6)*	*2 (0.2)*	*1 (0.2)*		
Nodal status					
0	188 (63.1)	495 (61.6)	319 (55.1)	9.754	0.045*
1-3	71 (23.8)	211 (26.3)	164 (23.3)		
≥4	39 (13.1)	97 (12.1)	96 (16.6)		
Not known	*11*	*15*	*11*		
NPI					
Good	134 (45.1)	337 (42.1)	203 (35.1)	13.230	0.01*
Intermediate	117 (39.4)	357 (44.6)	273 (47.2)		
Poor	48 (15.5)	106 (13.3)	106 (17.7)		
ER status					
Positive	224 (76.5)	595 (74.2)	435 (75.0)	0.592	0.744
Negative	69 (23.5)	207 (25.8)	145 (25.0)		
Not known	*16*	*16*	*10*		
Surgical management					
Conservation surgery	119 (38.5)	361 (44.1)	209 (35.4)	16.54	0.002*
Mastectomy	179 (57.9)	444 (54.3)	372 (63.1)		
Limited resection	*11*	*13*	9		
Method of diagnosis				19.667	0.001*
Symptomatic	225 (73.5)	504 (62.5)	420 (71.9)		
Screen detected	81 (26.5)	303 (37.5)	164 (28.1)		
Other	*3*	*11*	*6*		

*significant

Case notes were reviewed of all 1717 patients studied at a median time of 6.02 years following diagnosis. Most patients (1574) were followed up for over 5 years however, 143 were followed up for less than 5 years at the hospital of diagnosis. Search of the death registry revealed that none of these 143 patients were deceased. Therefore, in total 1283 (75.9%) patients were still alive at follow up. 434 patients were deceased.

At 5 year follow up of those that had 5 year follow up available, 308 patients were deceased. Overall, 5 year survival was 80.4%.

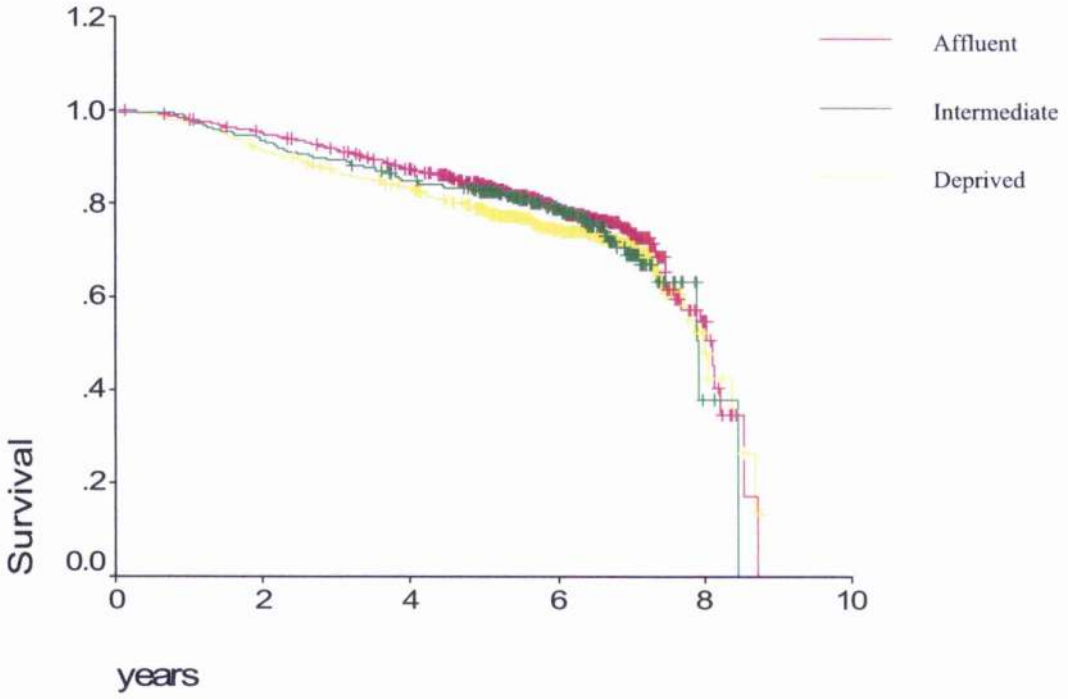
At 5 year follow up there was a trend for worse survival in the most deprived group compared with the most affluent and intermediate groups (77.8% vs. 82.4 % and 83.9% respectively). However on log rank testing this difference was not significant ($p = 0.20$) (see table 5 and graph 11).

Table 5: Cumulative survival by deprivation category

	1 year	2 year	3 year	4 year	5 year
Affluent	0.983	0.935	0.893	0.847	0.824
Intermediate	0.980	0.951	0.919	0.873	0.839
Deprived	0.973	0.915	0.866	0.833	0.778

Log rank: $p = 0.20$

Fig 11: Kaplan Meier curve of deprivation vs. survival



On Cox regression analysis deprivation did not predict survival ($p = 0.19$). Overall, age was a significant predictor of survival ($p<0.001$) with the worst survival in the in the youngest and oldest age groups and the best survival in the 45-54 age group (HR 0.38: 95% confidence interval 0.28-0.51; $p<0.001$).The difference in survival between the two youngest age group and the 65-74 age group was not significant. NPI was also significantly associated with survival ($p<0.001$) with significantly worse survival in the high NPI group compared with the low NPI group (HR 6.11: 95% confidence interval 4.64 – 8.04). ER status predicted survival ($p<0.001$), with ER negative having worse survival than ER positive tumours (HR 1.59: 95% confidence interval 1.29 – 1.94). Type of surgery also predicted survival ($p < 0.001$) with patients who had a mastectomy having worse survival (HR 1.85: 95 % confidence interval 1.51 – 2.27). If a patient had a symptomatic tumour they had worse survival than those diagnosed at breast screening ($p<0.001$; HR 2.22: 95% confidence interval 1.73-2.83). Year of surgery was not significantly associated with survival ($p = 0.63$).

Table 6: Univariate Cox regression survival analysis

	HR	95% confidence interval	P
Deprivation Category			
Affluent	1		0.19
Intermediate	0.90	0.69 – 1.18	
Deprived	1.09	0.86 – 1.43	
Age			
All age groups			<0.001
<25	1.96	0.27 – 14.0	0.50
25-34	1.36	0.73 – 2.51	0.33
35-44	0.60	0.42 – 0.85	0.004
45-54	0.38	0.28 – 0.51	<0.001
55-64	0.51	0.36 – 0.66	<0.001
65-74	1		
75+	1.42	1.07 – 1.87	0.012
NPI			<0.001
Good	1		
Intermediate	2.15	1.65 – 2.78	
Poor	6.11	4.64 – 8.04	
Oestrogen receptor status			<0.001
Positive	1		
Negative	1.59	1.29 – 1.94	
Type of surgery			<0.001
Conservation	1		
Mastectomy	1.85	1.51 – 2.27	
Year of surgery	1.02	0.92 – 1.14	0.63
How diagnosed			<0.001
Screening	1		
Symptomatic	2.22	1.73 – 2.83	

After adjusting for NPI, ER status and age group; deprivation, type of surgery and mode of presentation were not significant predictors of outcome. Age remained a significant independent predictor of survival ($p<0.001$) with the worst survival in the under 25age group. NPI was also a significant independent predictor of survival ($p<0.001$). Compared with the good prognosis group the poor prognosis group had a hazard ratio of death of 4.82 (95% confidence interval 3.53 – 6.58). ER status was also a significant independent predictor of survival ($p=0.005$), with ER negative tumours having a significantly worse prognosis (HR 1.38: 95% confidence interval 1.10-1.73).

Table 7: Multivariate Cox regression survival analysis

	HR	95% confidence interval	P
Deprivation Category			0.866
Affluent	1		
Intermediate	0.93	0.70 – 1.24	
Deprived	0.67	0.72 – 1.29	
Age			
All age groups			<0.001
<25	2.05	0.28 – 14.87	0.48
25-34	1.05	0.56 – 1.96	0.89
35-44	0.48	0.33 – 0.69	<0.001
45-54	0.40	0.29 – 0.55	<0.001
55-64	0.65	0.48 – 0.88	0.005
65-74	1		
75+	1.26	0.93 – 1.71	0.14
NPI			
Good	1		<0.001
Intermediate	1.67	1.26 – 2.21	
Poor	4.82	3.53 – 6.58	
Oestrogen receptor status			0.005
Positive	1		
Negative	1.38	1.10 – 1.73	
Type of surgery			0.06
Conservation	1		
Mastectomy	1.27	0.99 – 1.62	
Year of surgery	0.95	0.85 – 1.07	0.41
How diagnosed			0.29
Screening	1		
Symptomatic	1.18	0.87 – 1.6	

Discussion

This data shows that women from deprived areas presented with more advanced disease. They had larger tumours which were more likely to be node positive. In addition, they were more likely to have a mastectomy, and were less likely to be diagnosed at breast screening. However, despite worse pathology in the lowest deprivation category, deprivation did not predict survival. Significant predictors of survival were age, NPI, and ER status.

Clinicopathological features of the study population

The population studied were fairly typical. The majority were aged 45 to 64 (58.3%) which was partly a reflection of the inclusion of patients diagnosed at breast screening but also the demographics of the disease (124). The majority of patients in the study were from the intermediate deprivation category, with relatively few in the most affluent category. This is a reflection of levels of deprivation in Glasgow, which has some of the highest levels of deprivation in Britain (11).

The rate of mastectomy in the study group was surprisingly high, with just under 60% of patients undergoing mastectomy. This was despite over 60% of them having tumours less than 2 cm and over 97% of them having tumours under 5cm. The guidelines suggest that women with tumours under 5 cm should be considered for wide local excision unless they have a contraindication. It has been estimated that 10% of tumours smaller than 2cm (T1) and 30% of tumours between 2cm and 5cm (T2) require a mastectomy due to a medical contraindication (68). In the current study 46.3% of patients with T1 tumours and 77.9% with T2 tumours underwent mastectomy. The reasons for this high mastectomy rate and its relationship to deprivation are explored further in chapter two.

The majority of patients had symptomatic cancers (66.9%). However in the screening age group (aged 50-64) the majority of cancers were screen detected (60.1% screen detected vs. 38.9% symptomatic). The majority of cancers were of intermediate histological grade (48%) and were node negative (58.4%). In

comparison with data available from the NHSBSP(125), the proportions of patients with intermediate histological grade tumours were similar (48% in the study vs. 49% in the NHSBSP). There were more high grade tumours in the current study (29% vs 18% in NHSBSP) but this would be expected because the tumours in this study were both symptomatic and screen detected. Compared with the NHSBSP there were more node positive tumours in the current study (23% in NHSBSP compared with 39%). Again, this is a reflection of the inclusion of symptomatic tumours in this study.

Deprivation and tumour pathology

This study has shown that deprived women presented with more advanced tumours than the more affluent patient groups. This finding is not a new one. Several studies have reported differences in tumour pathology between socio-economic groups. (5;9;10;40;41;45;49;126;127). However, the association between late stage at presentation and deprivation has not been consistent (10;41;44;45;78). Studies from the USA have also suggested differences in tumours stage at presentation in socially disadvantaged groups, however, social status in the USA is inextricably linked with race and it is difficult to extract from the data which is the more important factor (128-130). The earlier studies did not define clearly what stage actually meant (5;126;128-130), which made them less reliable, although more recent studies have clearly defined that stage means larger, node positive tumours (10;40;44;45). The current study has the advantage that it has data on tumour size, nodal status and tumour grade and it agrees with recent studies which have shown that socially disadvantaged groups present later with more advanced tumours.

There has also been a suggestion that women from deprived areas are more likely to present with biologically more aggressive disease, in terms of tumour grade (40;41) or oestrogen receptor status (10), although these results have not been consistently replicated. The current study has shown that there was no significant difference in tumour grade or oestrogen receptor status between deprivation categories. The study by Thomson et al (10) was carried out in the pre-breast screening era when there was less ER positive disease (65% in the affluent group and 48% in the deprived group compared with 76 vs. 75 in the current study). This may be due to the tendency for

breast screening to identify slower growing ER positive tumours. In the current study there were more screen detected cancers in the affluent group so it would be expected that any differences in ER status would have been accentuated but this was not the case. The absence of a difference may be a reflection of changing patterns of risk factors for breast cancer, for example increasing use of hormone replacement therapy. This is discussed in more detail in chapter three.

Differences in histological grade between deprivation categories have been observed in two previous studies; however this study has not re-produced these results. Data on histological grade has not been routinely collected until relatively recently although the original grading by Bloom and Richardson was described in 1957 (131). In the study by Adams et al (40) deprivation was associated with less favourable histological grade but although they had more women in their study, grade was only available in 81.2% of patients at diagnosis. Equally, data on grade was only available in 82% of patients in the study by Taylor and Cheng (41), who also found an association with high grade and deprivation. The present study had histological grade available on over 99% of patients, which makes this data more reliable and suggests perhaps that the differences seen in the previously mentioned studies were a result of multiple comparisons rather than a genuine effect.

The reasons why people from deprived area should present with later stage tumours but not biologically more aggressive tumours are not clear. The larger size of the tumours may be related to a delay presentation to their GP. However, it has been previously reported that deprived patients with breast cancer are more likely to attend their GP practice (56). In addition, a meta-analysis looking at reasons for diagnostic delay in patients with breast cancer showed that low income was only a moderate predictor of diagnostic delay (55). The fact that the patients in the current study were more likely to have node positive disease may also be due to a diagnostic delay. It may also be a reflection of more aggressive disease, although there was no significant difference in histological grade or ER status between deprivation categories.

Although differences in stage at presentation have been previously described prior to the introduction of breast screening, this study shows that these differences continue

to exist. The introduction of breast screening should have helped to even out the differences in stage at presentation between socio-economic groups if all women attended, however, deprived women are less likely to attend breast screening. This has been shown in this study and agrees with findings in several other studies (32-35) and published data from the NHSBSP. Women from deprived areas in this study had larger, node positive tumours, rather than high grade, ER negative tumours which would suggest that these differences in tumour pathology are related to diagnostic delay or a symptomatic diagnosis rather than the development of more aggressive tumours.

The reasons why deprived women are less likely to attend breast screening are not obvious. Non-attendance at breast screening may be a reflection of difficulties in travelling to a breast screening unit, which are compounded by socio-economic deprivation. However, distance from a unit does not appear to affect attendance and screening uptake is greater in non-healthcare sites (35). So it appears that deprivation itself is more important than geographical location in determining attendance for screening mammography.

The current data have also shown that deprived women were more likely to have a mastectomy than more affluent women. This agrees with two previous studies (10;41). However, equally there have been studies which have suggested that there is no difference in surgical management between different socio-economic groups. This data has also shown that deprived women had larger tumours that tended to be node positive, so it is most likely that the choice of surgery was based on the tumour characteristics rather than unequal treatment for deprived and affluent women. This is discussed in greater detail in the following chapter.

Factors affecting survival

Age

As expected, age was a significant predictor of survival from breast cancer (table7). The distribution of hazard ratio of death was compared with the 65-74 years old age group and showed the survival was worst in the youngest age groups and the oldest age groups. In the two youngest age groups (under 25 and 25-34) the confidence

intervals are wide due to the small numbers of patients involved and therefore the difference in survival was not significant.

Nottingham Prognostic Index

NPI was a strong independent predictor of survival (table 7). The NPI has been extensively validated and is used routinely in the UK to determine adjuvant therapy as well as providing a basis for the assessment of newer tools to determine prognosis (132). In the original description of the NPI, it was divided into 3 groups(42). It was subsequently subdivided into 5 and more recently 6 groups(132). In this study NPI has been divided into three prognostic groups (good, intermediate and poor) because this is the clinical use of the NPI in Glasgow to determine adjuvant therapy.

Oestrogen Receptor Status

Oestrogen receptor status was also an independent predictor of survival (table 7). This agrees with previous studies. Although having an ER positive tumours itself does not confer a survival advantage, it does determine the response to hormonal manipulation which by extension improves survival (133).

The relationship between deprivation and survival

There were no survival differences between affluent and deprived women, despite the differences in tumour stage at presentation and mode of presentation. The univariate analysis of differences in five year survival approached significance but lost its significance on multivariate analysis.

The presence of a survival difference between socio-economic groups has been reported extensively. Initially, it was thought to be due to a paucity of data and inadequacies of data collection. However, with recent improvements in data collection at both regional and national levels, these deficiencies should have been reduced.

The reason why the current study has not demonstrated a survival gap is not clear. It may be due to a problem with small sample size. Previous studies have quantified the "deprivation gap" as between 6 and 7% difference in relative survival. However,

these studies involved substantially larger numbers of patients (5;6;9;19). Studies with comparatively similar numbers to the present study found a more modest survival gap and in some this was accounted for by differences in stage at diagnosis(8;89;134-136). Of the studies with similar numbers of patients there were further differences which might account for why they found a deprivation gap. Aziz et al found a significant difference in a small study of 286 patients in Pakistan. However, there is a greater difference in socioeconomic status between the most and the least affluent groups in Pakistan and healthcare is privately funded there (137). A study of 3920 patients in Switzerland identified a survival difference but again the Swiss healthcare system is privately funded so this might accentuate any differences (138). A further study from Australia which identified a deprivation gap based its measurement of deprivation on the location of the hospital of treatment (139). This provides a relatively crude measure of deprivation because it bases the comparison on large geographical units rather than small postcode sectors as in the current study. A recent study of 4645 patients in Sweden also identified a survival difference between rich and poor, measuring socioeconomic status by occupation or household income (140). However, in this study complete pathological data was not available for over a third of patients and had this been available, an association between socioeconomic status and survival might not have been found.

Thus there are several methodological reasons why other studies have demonstrated a difference and the current study has not. In agreement with this study, however, several others have found no difference in survival between affluent and deprived patients. A recent study of 3239 patients in the South East of England at 13 year follow up found that there was no survival difference (135). While a study of over 15,000 patients diagnosed between 1977 and 1997 in Sweden showed that there was a survival difference but this was accounted for by later stage at presentation and death from intercurrent disease (134). This agreed with the findings of two Scottish studies which found a survival difference but this was accounted for by differences in stage of disease at presentation (8;89).

The other reason that no survival difference has been demonstrated in this study may be due to length of follow up and inadequate numbers of patients. The median follow up was just over six years but this may not have been adequate to demonstrate

a survival difference between the most and least affluent groups. At 5 years the estimate relative survival for women in England and Wales is 80%. However, after this survival continues to fall with 20 year survival estimated at 64 % for women diagnosed between 2001 and 2003 (data from Cancer research UK website: www.info.cancerresearchuk.org). Therefore, although no survival difference was noted in this study it may be that there were not enough events to show an association between deprivation and survival. By the same token the number of patients in the study may not have been sufficient to show a survival difference. A recent Swedish study which examined a similar population of patients after the establishment of breast screening but with larger numbers of patients demonstrated a difference between the higher and the lower socio-economic groups(141). However, they only divided socioeconomic status into two groups which would have given a more homogenous group of patients and makes the results less reliable.

While the size of the study population and lack of long term follow up may have been the reason that no survival difference was seen in this group of patients, there may be other reasons for this. There may have been a genuine improvement in survival for the most deprived groups due to diagnostic or treatment factors.

Previously it has shown that differences in pathology between women of different socioeconomic groups might account for the deprivation gap. Evidence for this has been inconsistent and inconclusive. Two studies that noted a deprivation gap found that differences in stage at diagnosis only accounted for part of the difference (5;9), while a the study by Thomson et al found no difference in stage at presentation but found a difference in ER status which seemed to only account for 10 % of the deprivation gap (10). On the other hand, two Scottish studies showed that stage at diagnosis did account for survival differences (8;89). In fact, the current study has shown that pathology is significantly worse in deprived group but it did not appear to influence survival. This would tend to suggest that improvements in diagnosis of breast cancer are unlikely to be responsible for the narrowing of the deprivation gap. Deprived women were also less likely to be diagnosed at breast screening. Although diagnosis at breast screening predicted survival on univariate analysis, after correcting for age and tumour stage this relationship was no longer significant. Therefore, it seems unlikely that improvements in attendance at breast screening over

time have accounted for the improvements in survival in the most deprived patient group.

An alternative explanation is that there has been an improvement in breast cancer treatment that has narrowed the deprivation gap. The finding of this study that despite worse pathology deprived women did no worse than affluent women suggests that there may have been an improvement in the care specifically given to deprived women. Since the start of the breast cancer audit in Glasgow there has been a concerted effort to standardise treatment for patients. Every patient is treated by a specialist breast surgeon in a specialist breast unit. Following diagnosis each patient is discussed at the Multi-disciplinary team meeting which comprises the surgeon, oncologist, pathologist and radiologist as well as the breast care nurses. At the initial meeting treatment is discussed and planned. The patient is again discussed post operatively to assess what adjuvant therapy is needed. In this manner, any geographical variation is excluded as well as any disadvantage from not being treated by a specialist breast team.

Both treatment by a specialist surgeon (91;92;121;142) and geographical variation (48;90;143) have been shown to affect outcome . Being treated by a specialist surgeon with a large case load improves outcome partly because of access to chemotherapy and radiotherapy services via multidisciplinary team working but also due to better axillary staging and locoregional control (91;92;121;142). The fact that breast cancer surgery in Greater Glasgow has been centralised to specialist units may have eliminated the variability amongst surgeons and thus improved outcome not only for all patients but especially for more deprived groups and narrowed the deprivation gap.

It has been shown that geographical differences are partly due to the specialist surgeon working within the locale. However , even correcting for the caseload of the surgeon, deprivation and other clinical factors, geographical location still remains a significant predictor of survival (8;90;143). The explanation for this is not clear however, it seems likely that it is due to differences in the availability of adjuvant systemic treatment. Geographical differences in treatment that have previously been described were at health board level in Scotland (8;90) and at Health Authority level

in England (48;143) . The Greater Glasgow area may actually be too small to display any significant geographical variation so this may have only had a limited effect on changes to adjuvant treatment offered to patient in different parts of the city and thus may not have been responsible for the observed improvements in outcome for the most disadvantaged group.

Changes in adjuvant therapy may also have had a role in the improvement in survival for the most deprived patients. The data shown here have shown that women from the most deprived group were more likely to have larger node positive breast tumours so they may have been more likely to have had chemotherapy. Unfortunately, data on the use of adjuvant therapy was not available for this cohort of patients. Several studies have shown the superiority of anthracyline based chemotherapy regimes over the CMF chemotherapy regime which was previously in routine use. The recent Oxford overview showed the survival advantage to be 4% with anthracylines over CMF (133). Anthracyline based chemotherapy has become part of routine adjuvant treatment in Greater Glasgow since the mid to late 90's and prior to this it was only available in the context of clinical trials. It may, therefore, have had some effect on the improvement in survival in the deprived patients but this effect is likely to be small and difficult to quantify without data on adjuvant therapy.

Host factors may also have played in role in the reasons why deprived patients with breast cancer are doing better and nothing to do with the way breast cancer is diagnosed or treated. In fact, a study by MacLeod et al which was done prior to the setting up of the Breast Cancer Audit showed that there was no difference in the surgical and oncological care that patients received regardless of socio-economic status(56). In addition, although recent evidence has shown that as the gap in wealth between rich and poor has grown and so has the gap in life expectancy, on closer examination the difference in life expectancy has remained stable in women while getting wider in men (11). This is borne out by a recent study which looked at the differences in breast cancer mortality between affluent and deprived women which showed the gap to be static (19). The absence of a survival difference in the present study may be due to deprived women actually becoming healthier and therefore not dying from intercurrent disease.

Conclusion

The previously described differences in survival between women from affluent areas and women from more deprived areas have not been demonstrated in this study. Although, women from deprived areas had larger tumours and were more likely to have node positive disease, this had no apparent effect on survival. Deprived women were less likely to attend breast screening and were more likely to have a mastectomy, however this also had no effect on survival.

While the absence of a survival difference may be due to insufficient numbers in this study or inadequate length of follow up, it may be due to improvements in the diagnosis and particularly treatment of breast cancer. Breast cancer services in Glasgow are delivered in the context of a multidisciplinary team which may have helped to even out geographical variation and variation between surgeons. Alternatively the survival improvements in the most deprived group may be a reflection of overall improvements in health.

Chapter 2

Does deprivation affect breast cancer management?

Introduction

The findings of the previous chapter have suggested that the previously observed deprivation gap (10;19) no longer exists in Glasgow. However, several other factors were shown to be different between affluent and deprived women. Deprived women appeared to have more advanced tumours at presentation, they were less likely to attend breast screening and they were more likely to have a mastectomy. The increased mastectomy rate in deprived patients may be a reflection of more advanced tumours in this group of patients, but it to what extent is it a reflection of different treatment in secondary care.

Trials have shown no long term survival advantage from mastectomy over breast conservation surgery for tumours up to 5 cm (62;63;144). Despite this mastectomy rates remain higher than expected (71). There does appear to be a higher rate of local recurrence in the patients who have conservation surgery and this is particularly seen with long term follow up and particularly in young women (145). This does not, however, affect survival. The reasons for the low uptake of mastectomy are not immediately obvious.

The relative contraindications to conservation are well documented: multifocal tumours; 1st or 2nd trimester of pregnancy; history of previous irradiation to the affected breast; or a large tumour in a small breast that would result in an unacceptable cosmetic result. However, it is estimated that only a small proportion of all breast cancers will require a mastectomy for a medical reason(146). Unnecessary mastectomy can be associated with excess psychological co-morbidity (83) , particularly if the patient does not perceive that she had a choice in the decision for surgical treatment (84).

The disparity in mastectomy rate between affluent and deprived women is well documented in studies from the USA, where healthcare is privately funded (38;72;75-77). However, these differences are not so well demonstrated in UK populations where healthcare is publicly funded (10;41). Glasgow is known to have high levels of deprivation (11) and had anecdotally been noted to have a high mastectomy rate. The aim of this chapter is to measure the mastectomy rate in Glasgow. If the mastectomy rate is higher than expected this might be a reflection of high levels of deprivation. In addition, to what extent were surgeons were influencing women in their choice of surgical management?

Methods

Using data from the Greater Glasgow Breast Cancer Audit database (see previous chapter for description of data collection methods), patients who were diagnosed between 1996 and 2001 were analysed. Patients were treated in one of five hospitals in Glasgow (Glasgow Royal Infirmary, Western infirmary Glasgow, Stobhill Hospital, Southern general Hospital and Victoria Infirmary Glasgow). Each hospital has a specialist breast unit staffed by a multidisciplinary team.

Only patients with primary operable breast cancer were included. Those with tumours greater than 5 cm (on pathological reporting) and those with locally advanced disease unsuitable for mastectomy were excluded from the analysis. Data on tumour pathology (size, grade, nodal status and ER status) was recorded. Surgical management was divided into "conservation surgery," (lumpectomy with axillary staging) and "mastectomy" (mastectomy with axillary staging). Patient's age and deprivation category were also recorded. Deprivation was determined using the method of Carstairs and Morris (14). Categories 1 and 2 were combined to "affluent"; 3, 4 and 5 were combined to "intermediate"; and 6 and 7 were combined to "deprived".

All data was entered onto SPSS for Windows version 9 (SPSS, Chicago, IL). Univariate analysis was performed using χ^2 tests of association. Age, deprivation, tumour size, nodal status, histological grade, oestrogen receptor (ER) status and hospital were individually examined for their association with surgical management. Univariate analysis using χ^2 tests of association was also performed to identify which factors were significantly related to deprivation. Those factors that were significantly related to surgical management on univariate analysis were then entered into the multivariate model and subjected to stepwise logistic regression analysis to identify those factors which were independent predictors of surgery.

No ethical permission was required because this was an analysis of a retrospective cohort of patients.

Results

Of the 3570 patients entered onto the database 3419 had tumours smaller than 5cm. The characteristics of the study population are shown in table 7 below. Of the patients with tumours<5 cm, 1588 (46.4%) underwent conservation surgery and 1831 (53.6%) mastectomy. The majority were in the screening age group (50-64). The majority were of intermediate dep cat (48.5%). Most had tumours between 10 and 19 mm (39.4) that were node negative (58.1%), grade II (44%) and ER positive (74.6%). 63.9% had symptomatic tumours and the majority were treated at hospitals 1 and 4, (40.3% and 28.4%, respectively). There was an approximately even spread of patients over the years studied

Over the time period examined, the mastectomy rate decreased while the rate of conservation increased (fig 12).

On univariate analysis, deprived women were more likely to have a mastectomy ($p<0.001$). In addition, increasing tumour size was significantly predictive of having a mastectomy ($p<0.001$). Patients with positive nodes were also significantly more likely to have a mastectomy ($p<0.001$). High grade also predicted mastectomy ($p<0.001$) as did having a symptomatic cancer ($p<0.001$). The mastectomy rate also varied significantly between hospitals ($p<0.001$) (table 8).

Deprivation was significantly associated with having a larger tumour ($p<0.001$). Deprived women were less likely to be diagnosed at breast screening ($p<0.001$) (table 9). There was no significant association between deprivation and nodal status ($p=0.075$), ER status ($p=0.078$) or grade ($p=0.282$) (table 9).

Step wise logistic regression modelling showed that deprivation maintained its significance when age and year of surgery, hospital of diagnosis were added into the model (OR=1.12; $p=0.02$) (table 10) but lost its significance when tumour size and was added to the model (OR=1.09; $p=0.11$). The multivariate analysis showed that age, year of surgery, tumour size, nodal status, histological grade, method of diagnosis, and hospital were independently predictive of surgical management (table 11).

Table 7: Characteristics of the study population

Characteristic	Number	%
Surgery		
Conservation surgery	1588	46.4
Mastectomy	1831	53.6
Deprivation		
Affluent	615	18.0
Intermediate	1657	48.5
Deprived	1147	33.5
Age group		
<40	186	5.4
40-49	517	15.1
50-64	1704	49.8
65-74	667	19.5
75+	345	10.1
Tumour size (mm)		
<10	518	15.2
10-19	1348	39.4
20-29	944	27.6
30-39	441	12.9
40-49	168	4.9
Nodal Status		
Negative	1986	58.1
Positive	1317	38.5
Missing	116	3.4
Oestrogen receptor status		
Positive	2552	74.6
Negative	704	20.6
Missing	163	4.8
Grade		
I	774	22.6
II	1515	44.3
III	1097	32.1
Missing	33	1.0
Method of diagnosis		
Screen detected	1235	36.1
Symptomatic	2184	63.9
Hospital		
1	1378	40.3
2	539	16.8
3	291	8.5
4	972	28.4
5	239	7.0
Year of surgery		
1996	517	15.1
1997	582	17.0
1998	543	15.9
1999	582	17.0
2000	648	19.0
2001	547	16.0

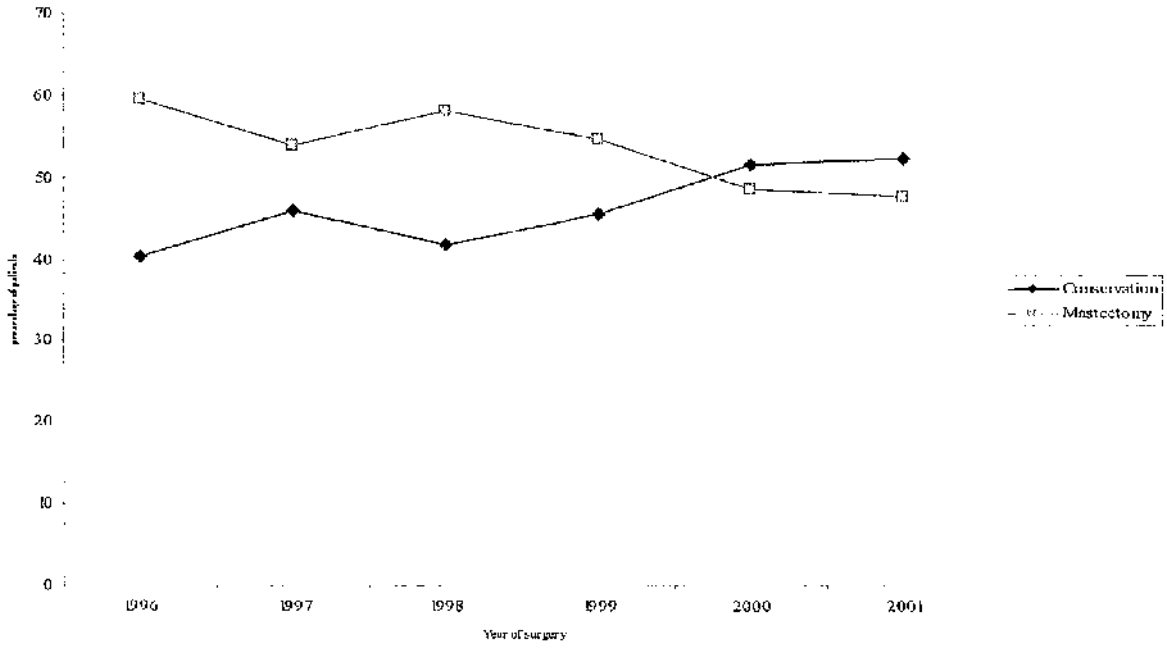


Fig 12: Percentage of patients having mastectomy or conservation for the years 1996-2001.

Table 8: Univariate analysis of factors determining surgical management

Variable	*Conservation (%) N=1588 (46.4)	†Mastectomy (%) N=1831 (53.6)	χ^2	p
Deprivation				
Affluent	285 (46.3)	330 (53.7)	17.301	<0.0001
Intermediate	824 (49.7)	833 (50.3)		
Deprived	479 (41.8)	668 (58.2)		
Tumour size (mm)				<0.0001
<10	380 (73.4)	138 (26.6)	472.492	
10-19	770 (57.2)	577 (42.8)		
20-29	330 (35.0)	614 (65.0)		
30-39	90 (20.4)	351 (79.6)		
40-49	17 (10.1)	151 (89.9)		
Nodal Status				
Negative	1117 (56.2)	869 (43.8)	252.172	<0.0001
Positive	390 (29.6)	927 (70.4)		
Not known	*81*	*35*		
Method of diagnosis				
Symptomatic	409 (33.2)	824 (66.8)	327.684	<0.001
Screen detected	1396 (65.4)	737 (34.6)		
Not Known	*26*	*26*		
Grade				
I	507 (65.5)	267 (34.5)	158.889	<0.0001
II	667 (44.0)	848 (56.0)		
III	402 (36.6)	695 (63.4)		
Not Known	*12*	*21*		
Hospital				
1	722 (52.4)	656 (47.6)	65.751	<0.0001
2	198 (36.7)	341 (63.3)		
3	95 (32.6)	196 (67.4)		
4	472 (48.6)	500 (51.4)		
5	101 (42.3)	138 (57.7)		

††Defined as lumpectomy with axillary staging
† Defined as mastectomy with axillary staging

Table 9: Univariate analysis of association between deprivation and tumour characteristics.

Variable	Affluent (%) N=615 (18.0)	Intermediate (%) N=1657 (48.5)	Deprived (%) N=1147 (33.5)	χ^2	P value
Tumour size					
<10	101(16.4)	279(16.8)	138(12.0)	31.699	< 0.0001
10-19	250(40.7)	673(40.6)	425(37.1)		
20-29	160(26.0)	448(27.0)	336(29.3)		
30-39	77(12.5)	191(11.5)	173(15.1)		
40-49	27(4.4)	66(4.0)	75(6.5)		
ER status					
Positive	487(79.2)	1262(76.2)	846(73.8)	8.405	=0.078
Negative	112(18.2)	337(20.3)	267(23.3)		
Not known	*16*	*58*	*34*		
Nodal status					
Negative	364(59.2)	988(59.6)	634(55.3)	8.484	=0.075
Positive	224(36.4)	619(37.4)	474(41.3)		
Not known	*27*	*50*	*39*		
Method of diagnosis				55.476	<0.0001
Screen detected	204(33.2)	700(42.2)	331(28.9)		
Symptomatic	411(66.8)	957(57.8)	816(71.1)		
Grade					
I	140(22.8)	380(23.0)	254(22.1)	5.051	=0.282
II	245(44.9)	755(45.6)	485(42.3)		
III	191(31.2)	510(30.8)	396(34.5)		
Not Known	*7*	*10*	*12*		

Table 10: Multivariate analysis of demographic factors determining surgical management.

	Relative risk of mastectomy (95% CI)	P
Deprivation		0.02
Affluent	1	
Intermediate	0.89 (0.73-1.09)	
Deprived	1.12 (0.90 - 1.38)	
Age		<0.001
<40	1.39 (1.02 – 1.90)	
40-49	1.77 (1.44-2.17)	
50-64	1	
65-74	2.47 (2.04 – 2.48)	
75+	4.01 (3.06-5.25)	
Year of surgery		<0.001
1996	1.65 (1.29-2.14)	
1997	1.32(1.03-1.68)	
1998	1.66(1.29-2.13)	
1999	1.32 (1.04-1.69)	
2000	1.04 (0.82-1.32	
2001	1	
Hospital		<0.001
1	1	
2	1.41 (1.02-1.95)	
3	0.84(0.63-1.13)	
4	1.89(1.30-2.74)	
5	1.06(0.78-1.44)	

Table 11: Multivariate analysis of factors determining surgical management.

Variable	Relative risk of Mastectomy (95% CI)	P
Deprivation		=0.22
Affluent	1	
Intermediate	0.95 (0.76 – 1.19)	
Deprived	1.12 (0.88 – 1.43)	
Age group		
<40	1	<0.001
40-49	1.28 (0.78 -1.87)	
50-64	1.39 (0.98-2.00)	
65-74	2.36 (1.62-3.44)	
75+	4.60 (2.91-7.2)	
Tumour size (mm)		<0.001
<10	1	
10-19	1.41 (1.08 - 1.82)	
20-29	2.55 (1.91 -3.40)	
30-39	4.49 (3.11 - 6.49)	
40-49	13.47 (6.98-26.02)	
Nodal Status		
Negative	1	<0.001
Positive	1.90 (1.60 – 2.26)	
Oestrogen receptor status		=0.27
Positive	1	
Negative	1.3 (0.91-1.42)	
Grade		<0.001
I	1	
II	1.54 (1.24 – 1.90)	
III	1.74 (1.35 – 2.24)	
Method of diagnosis		<0.001
Screen detected	1	
Symptomatic	2.13 (1.72 – 2.64)	
Hospital		
1	1	<0.001
2	1 .20 (0.93 – 1.55)	
3	1.32 (0.95 – 1.85)	
4	1.41 (1.16 – 1.73)	
5	0.62 (0.44 – 0.87)	
Year of surgery		<0.001
1996	1.91 (1.42 – 2.57)	
1997	1.42 (1.07 – 1.89)	
1998	1.76 (1.32- 2.35)	
1999	1.40 (1.05 – 1.87)	
2000	1.08 (0.82 – 1.44)	
2001	1	

Discussion

These data show that the mastectomy rate in Glasgow is higher than expected (68). On univariate analysis, deprived women were more likely to have a mastectomy than more affluent women, however they were also more likely to have larger symptomatic tumours which may explain why this association was not significant on multivariate analysis. Mastectomy rates were also found to be different between hospitals.

The mastectomy rate of just under 54% which has been demonstrated in this study, although higher than expected is probably appropriate. There is a wide variation in the rate of mastectomy (69;70) reported in the literature. The recent ATAC trial also looked at the variation in mastectomy rates internationally and showed that the rate of mastectomy in the UK as a whole is 42%, 12% less than the rate demonstrated here. In fact the ATAC trial (53) recruited patients from centres with active research programmes which would suggest that these patients were being offered state-of-the art treatment so in practice the mastectomy rate in the UK as a whole is probably higher than 42%. In addition, only women with ER positive tumours were included in the ATAC trial, these tend to be smaller than ER negative tumours. In the current study the mastectomy rate for ER positive women was 52% so the mastectomy rate in the ATAC trial may have been artificially low.

Based on figures from the United States, it has been estimated that 10% of tumours smaller than 2cm and 30% of tumours between 2cm and 5cm require a mastectomy due to a medical contraindication (68). In our study the percentages having a mastectomy were 38% and 72% respectively. This database does not identify which patients have a medical contraindication to conservation surgery but it is unlikely that a high incidence of medical contraindications would explain the relatively high mastectomy rate. It may be patient choice that is causing the high mastectomy rate. Several reasons have been suggested for why patients might choose mastectomy over conservation surgery. Access to radiotherapy sites has been suggested as a strong determining factor due to the time involved and the travelling and childcare costs incurred (80). Attendance for post-operative radiotherapy involves 5 to 6 weeks of

therapy. In Glasgow, access to radiotherapy is equal for all patients, however, it may involve increased costs in terms of childcare which may influence some patients to avoid it by opting for mastectomy. There may also be a perception that local excision of the tumour does not constitute definitive treatment and this might influence the women to choose mastectomy instead. These attitudes are more prevalent in less educated women of lower socio-economic status (79). Alternatively it may be the attitude of the surgeons themselves to breast conservation surgery that influences the high mastectomy rate.

In the univariate analysis, this data has shown that women from deprived areas were more likely to have a mastectomy than women from more affluent areas. This may be a reflection of some of the above reasons why women choose mastectomy, for example, the inconvenience of radiotherapy, fear of local recurrence or the surgeon's recommendation. However, this data has also shown that women from deprived areas had larger and symptomatic tumours. On multivariate analysis of demographic factors alone, deprivation was an independent predictor of mastectomy, however when tumour size was added to the model it lost its significance. This suggests that the tumour size is the most important predictor of mastectomy and that the association seen between deprivation and mastectomy was a reflection of larger tumours rather than biased treatment.

Previous studies have been inconsistent in showing a difference in tumour size between affluent and deprived women. Several have shown no difference (10;41;45;78;120), while one study showed that deprived women presented with more advanced disease but no comment was made on tumour size (40). Part of the reason for this difference in tumour size might be explained by screening uptake. In the current study, deprived women were less likely to be diagnosed at breast screening and were more likely to present with symptomatic cancers. The uptake of breast screening in Glasgow is 68.1% (data from Scottish Breast Screening Programme) with the lowest uptake in the most deprived groups. This is not specific to Glasgow but has been noted previously (33). Alternatively the development of bigger tumours in deprived women could be a reflection of more aggressive disease. This data failed to show an association between deprivation and ER negative tumours, although they approached significance. Previous studies have in fact shown

this to be the case (10) and perhaps had there been more patients included a similar result would have been demonstrated here. The reasons for the differences in tumour pathology have been discussed in the previous chapter and will not be repeated here.

Screen detected tumours tend to be smaller than symptomatic tumours however, being diagnosed at breast screening was predictive of conservation surgery independent of tumour size so this is probably reflective of screen detected tumours being impalpable. Deprived women were less likely to attend breast screening so this may also have contributed to their higher mastectomy rate in the univariate analysis.

It is interesting to note that pathological factors also determine surgical management. It is not surprising that patients with larger tumours are more likely to have a mastectomy, however, what is surprising is the number of patients with relatively small tumours (<2 cm) who had a mastectomy. It may well have been patient choice that determined this but the database does not identify whether these patients had a contraindication to conservation surgery (for example multicentric disease). Interestingly, positive nodes were also associated with an increased likelihood of mastectomy, independent of tumour size. This finding agrees with that of Morrow et al (68). Palpable nodes on clinical examination is an indication for adjuvant therapy and not a contra indication to conservation surgery but the association of axillary node involvement with likelihood of mastectomy suggests that surgeons may feel that mastectomy is the more "aggressive" treatment for advanced disease. Histological grade was also associated with increased likelihood of mastectomy on multivariate analysis. The reason for this is not entirely clear. Histological grade is not routinely assessed pre-operatively so should not affect surgical management.

The populations served by the different hospitals are similar in age and access to radiotherapy services although their levels of deprivation differ. Despite this, the variation in mastectomy rates between hospitals was quite marked. The rate was lowest in hospital 1 (47.6%) and highest in hospital 3 (67.4%). Part of this variation was due to the large breast screening practice in hospitals 1 and 4. However, in the multivariate model, which included method of diagnosis, hospital of treatment was independently predictive of surgical management. The relative risk of mastectomy

varied from 0.62 in hospital 5 to 1.41 in hospital 4 when correcting for other pathological and demographic factors. All patients were treated in specialist units by a multidisciplinary team, however, it is the surgeons' recommendations that are most important in determining treatment. Not all women will be offered a choice of surgery because they have a contraindication to mastectomy. Of those that do have a choice, some will choose mastectomy despite being suitable for conservation but these patients are in the minority and most will take the surgeons' advice (73;79;147;148). The wide variety in mastectomy rates is therefore likely to be a reflection of individual surgeon's practices and it is the individual surgeons who have an influence over choice of surgical management. Although guidelines have been produced recommending suitability for conservation surgery (67;149), the wide variability suggests a lack of consensus.

Variation between surgeons has been previously described. It has been suggested that conservation rates are lower in older surgeons, and male surgeons (39;148) although this finding has been inconsistent. It has also been suggested that non-specialist surgeons and those working outside a teaching hospital are more likely to perform mastectomies(150). In addition, a high volume of patients also contributes to a lower mastectomy rate(39). Several of the units in Glasgow have more than one consultant surgeon working in them and the database does not identify each individual surgeon, so it is difficult to tell how much each of the above factors has influenced surgical decision making. All of the units are staffed by consultant surgeons with a declared specialist interest in breast surgery, so specialisation is unlikely to be a factor. Volume of patients is also unlikely to be important because hospital 5 had the smallest volume of patients but had the lowest relative risk of mastectomy. The demographics of the population served by each hospital are different but hospital was still an independent predictor of surgical management. The fact that there were only 5 units included in this study makes it difficult to generalise about what features of each unit might influence the mastectomy rate. The most likely explanation is that the variation in mastectomy rate is down to the individual surgeons' personal preference.

Variability in mastectomy rates and unnecessary mastectomy may result in excess psychological co-morbidity. In addition, if the unnecessary mastectomies are being

performed in women from deprived background they will be doubly disadvantaged because they are more likely to have a worse outcome anyway from their poorer prognosis tumours. Initial work showed that similar rates of anxiety, depression and sexual problems were seen in patients who had mastectomy and conservation surgery (82). It was then thought that having a choice of surgery might be the important factor in determining who developed psychological co-morbidity (151), but later still it was thought that it was the communication style of the surgeon that was the most important factor (84). A more recent prospective, randomised trial with longer term follow up suggested that in fact rates of psychological co-morbidity were lower in patients who had had conservation surgery (83). There is evidence that some psychological factors improve with time (152) and the reason that early studies did not show a difference may have been due to insufficient follow up that was too short to demonstrate any long-term co-morbidity.

A recent study in Glasgow showed that women from deprived areas were more likely to display psychological co-morbidity, in terms of greater anxiety, than more affluent women. Although deprived women have greater psychological co-morbidity unrelated to their cancer diagnosis, they also suffer psychological co-morbidity due to a lack of information given to them by their hospital specialists and breast care nurses(87). This would suggest that deprived women might be more susceptible to psychological co-morbidity in two ways, the need for a mastectomy due to larger tumours, and also because they do not receive enough support post-operatively from the specialist breast team.

Conclusion

The mastectomy rate in Glasgow is higher than that reported for the rest of the UK. Deprived women were found to have more mastectomies than affluent women. However, they also had larger, symptomatic tumours. The high mastectomy rate in deprived women was, therefore, a reflection of them having larger tumours rather than biased treatment of them and the high mastectomy rate was, in part, a reflection of high levels of deprivation in Glasgow. It does appear that women from deprived areas are being treated appropriately and the choice of surgery is based on tumour characteristics. There was a significant variation in the mastectomy rate between hospitals which suggests that there still remains a lack of consensus on the optimal surgical management of early stage breast cancer.

Chapter 3

The changing pattern of oestrogen receptor positive breast cancer

Introduction

The pattern of incidence of breast cancer seems to be changing. In Scotland incidence has risen from 84.8/100,000 person-years at risk (European standard population) in 1980 to 118/100,000 person-years at risk in 2003. This increase has been essentially linear except for a period in 1990-1993 where there was a sharp increase due to the introduction if breast screening. Data from the West Midlands has suggested that the increase in incidence is different for different socio-economic groups, with an increasing incidence in affluent women and a relatively constant incidence in deprived women (see fig 6) (20). Despite the increasing incidence, mortality is falling. The mortality rate for Scotland in 1980 was 45.4/100,000 compared with 41.1/100,000 in 2003. There has also been an improvement in 5-year survival, from around 60 % between 1977 and 1981 to around 80% between 1997-2001 (data from ISD Scotland). While part of the survival benefit might be attributed to breast screening or improvements in treatment, other factors may also play a role.

The answer may come from the changing pattern of hormone sensitivity in breast cancer. Two previous studies from the USA have shown an increasing incidence of ER positive breast cancer (153;154). Even without systemic therapy oestrogen receptor (ER) positive breast cancer has a lower incidence of early recurrence compared to ER negative breast cancer(133). Additionally, ER positive cancers respond to endocrine manipulation, with agents such as tamoxifen, reducing the likelihood of recurrence and with the subsequent improvements in survival (133). Potentially, an increase in incidence of ER positive breast cancer compared with ER negative breast cancer might contribute to improvements in survival

The risk factors for breast cancer are well documented, late age of first birth, nulliparity, early menarche, late menopause and use of HRT. All of these factors centre around exposure to oestrogen. More recently attempts have been made to identify if the risk factors for ER positive breast cancer and ER negative breast cancer are distinct and there is mounting evidence that this is the case. Increased risk of ER positive breast cancer is specifically associated with early menarche, nulliparity, delayed childbirth (155-159). In addition, HRT has been shown to not only increase the risk of breast cancer overall (27), but more so in ER positive tumours(160). Adult obesity is also known to be associated with an increased risk of ER positive breast cancer (161), while childhood obesity appears to be relatively protective (162).

The incidence of these risk factors for oestrogen receptor positive breast cancer appears to be increasing. Age at menopause has increased while age at menarche has decreased (25). More women are nulliparous or have an older age at first live birth (154). Use of hormone replacement therapy has increased (27), as have adult and childhood obesity (163). Moreover, there is a difference in the incidence of these risk factors between socio-economic groups. Women of higher socioeconomic status have a higher age at first birth with a higher incidence of nulliparity. They tend to have a shorter duration of breast feeding and have a later menopause (4). In addition, they are more likely to take HRT (28). This raises the question of whether changes in the biology of breast cancer (as determined by the ER status) could account for the changing pattern of incidence and the differences in outcome between affluent and deprived women.

Hormonal status of breast cancers can be determined using immunohistochemistry (IHC) or ligand binding assay (LBA). Until the 90's LBA was the only method in routine clinical use, this was then superseded by IHC, which was quicker, required less tissue, and did not use radioactive isotopes. IHC is also more sensitive and specific than LBA, with a difference in sensitivity of around 10% (164;165). Two previous studies based on data from the USA have suggested that although the incidence of breast cancer has increased, there has been a disproportionate increase in ER positive tumours(153;154). One reported a 6 % increase between 1973 to

1977 (153) and the other a more modest increase of just over 2% between 1992-1998 (154) .

In this chapter, data on ER status obtained from women diagnosed between 1980 and 1988 determined by LBA, before the introduction of breast screening, is analysed and compared with a group of women diagnosed in 1996 –2001, who had ER status determined by IHC, after the introduction of breast screening. It was likely that the later group would have a greater proportion of hormone sensitive tumours due to the differences in technique; however, the hypothesis of this chapter is that this increase in the proportion of ER positive tumours would not be accounted for solely by differences in technique. In addition, if there had been an increase in the proportion of ER positive tumours, was it greater in affluent women compared with deprived women?

Methods

The study compares two cohorts of patients who presented with primary operable invasive breast cancer. The first cohort was symptomatic and was diagnosed between 1981 –1988. The second cohort was both symptomatic and screen detected and was diagnosed between 1996-2001.

In the early cohort, 2423 patients were diagnosed at 4 different hospitals and were entered into the analysis. This cohort represents all patients diagnosed at these 4 hospitals during the time period examined, who had ER status determined by ligand binding assay (LBA). ER status was determined at the time of surgery in one laboratory by LBA on the cytosolic fraction, using standard techniques as described elsewhere (166). This laboratory was subject to External Quality Assessment (EQA). Tumours with an ER content of 20 fmol/mg protein were considered to be ER positive and likely to respond to endocrine therapy.

In the later cohort, 3115 patients were diagnosed at the same 4 hospitals and had ER status determined by IHC. These patients were from the Greater Glasgow Breast Cancer Audit database, which has been used in the preceding two chapters. Patients from hospital five were excluded as there were no patients for this hospital in the early cohort. IHC was performed on each patient using standard techniques (167) in 2 different laboratories (at hospitals 1 and 4). 10% positive staining was taken as the lower limit of ER positivity. The IHC methods were identical in both laboratories and were subject to EQA.

Patient age was also recorded as well as method of diagnosis (screen detected or symptomatic) hospital of diagnosis, deprivation category. Deprivation was determined using the method of Carstairs and Morris(14). The seven dep cats were combined to "affluent" (1 and 2), "intermediate" (3, 4 and 5) and "deprived" (6 and 7).

All data was entered onto SPSS for Windows version 9 (SPSS, Chicago, IL). Univariate statistical analysis was performed using χ^2 tests of association. Age,

deprivation, hospital of diagnosis and time period of diagnosis were individually examined to assess whether they were associated with having an ER positive tumour in each time period.

Those factors that were significantly associated with likelihood of having an ER positive tumour were entered into the multivariate model and analysis was performed using stepwise logistic regression analysis to identify which factors were significantly predictive of ER status.

Ethical permission was not sought because this was a retrospective analysis of two cohorts of women in whom data had already been collected.

Results

In the early cohort contained 2152 patients, of these 1078 (50.1%) had an ER positive tumour. In the later cohort 2471 (79.3%) of 3115 patients had ER positive tumours. This difference was statistically significant ($p<0.0001$). There were 174 patients diagnosed in the late time period who did not have data on ER status available and these patients were excluded

There was no significant change in percentage of ER positive tumours over the years of the early time period (χ^2: $p = 0.11$) see fig 13. There was, however, significant variation in percentage of patients with an ER positive tumour between years in the late time period (χ^2:$p<0.001$)

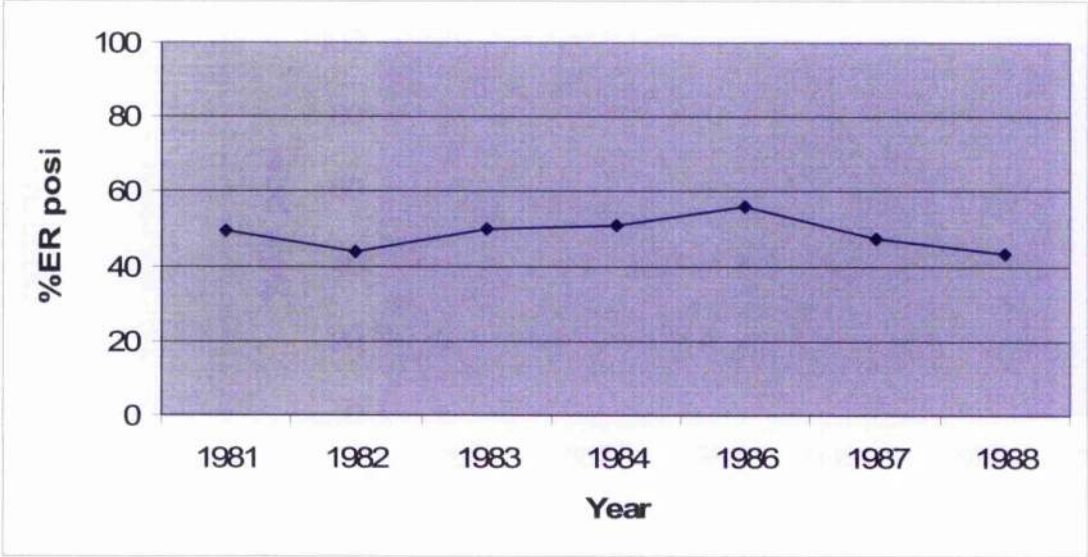


Fig 13: Percentage of ER positive tumours in each year of the early time period

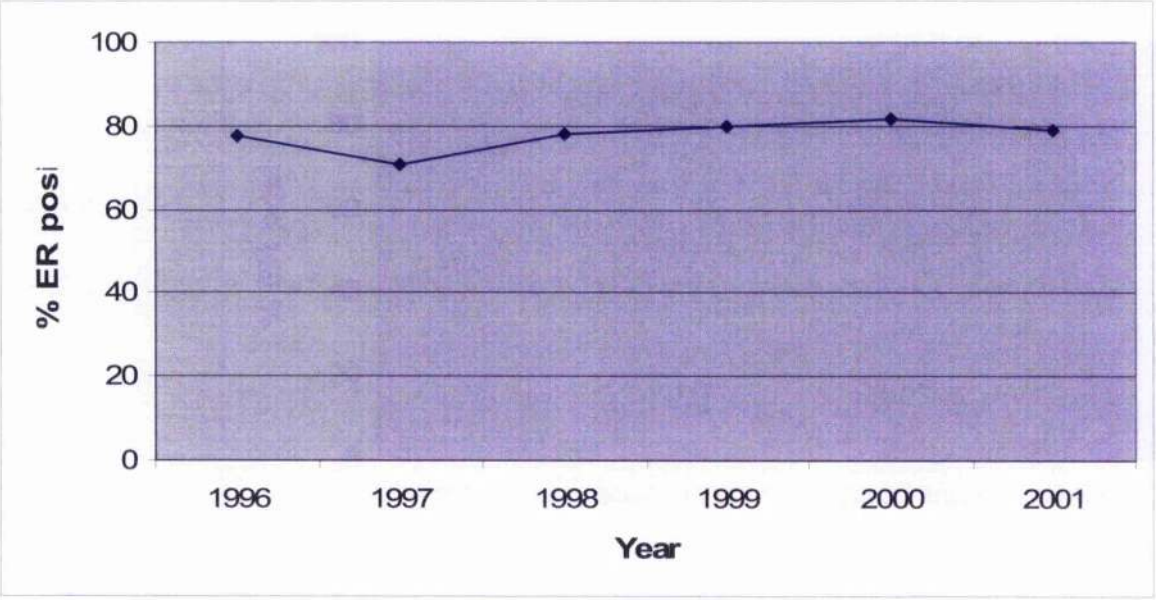


Fig 14: Percentage of ER positive tumours in each year of the late time period

Demographics of the 2 study groups

The demographics of the study groups differed significantly with respect to age (χ^2: $p<0.0001$), and deprivation category (χ^2: $p<0.0001$) (see table 12).

Table 12: Comparison of population demographics

		Early	Late
Age group	<39	148 (6.9)	169 (5.1)
	40-49	373 (17.3)	464 (14.9)
	50-64	856 (39.8)	1588 (51.0)
	65-74	508 (23.6)	584 (18.7)
	75+	267 (12.4)	319 (10.3)
P <0.0001*			
Deprivation Category	Affluent	432 (20.1	574 (18.4)
	Intermediate	789 (36.7)	1550 (49.8)
	Deprived	931 (43.3)	991 (31.8)
P<0.0001*			

*P values derived from χ^2 tests of significance

The patients in the later cohort had significantly smaller tumours compared with the early cohort (χ^2: p<0.001). Patients in the later cohort were more likely to have node negative tumours than the early cohort (χ^2: p<0.001) (see table 13)

Table 13: Comparison of tumour characteristics in the two cohorts

		Early cohort	Late cohort
Tumour size	<10	58 (4.7)	478 (15.3)
	10-19	310 (25.2)	1242 (39.9)
	20-29	365 (29.7)	811 (26.0)
	30-39	209 (17.0)	352 (11.3)
	40-49	109 (8.9)	136 (4.4)
	50+	179 (14.6)	96 (3.1)
	Missing	*724*	0
P<0.001			
Nodal status	Negative	589 (34.8)	1814 (60.1)
	1-3 nodes	598 (35.3)	765 (25.4)
	4 or more nodes	236 (29.9)	437 (14.5)
	Missing	729	99
P<0.001			

Univariate Analysis

Effect of Age

Increasing age was associated with an increased likelihood of having an ER positive tumour (p<0.0001). This association remained when considering each time period separately. The proportion of ER positive tumours increased in all age groups over time (table 14).

Effect of deprivation

Deprivation was not associated with likelihood of having an ER positive tumour in either the early or the late cohort (χ^2: p = 0.170 and 0.187 respectively) (table 14).

Variation between hospitals.

In the early cohort the variation in the proportion of ER positive tumours in each hospital was not significant on univariate analysis. In the later cohort there was significant variation in the proportion of ER positive tumours between hospitals ($p = 0.009$) (table 14).

Multivariate analysis

On multivariate analysis, patients diagnosed in the later time period were more likely to be ER positive (RR 3.22 $p<0.0001$). This was independent of age, hospital or method of diagnosis or deprivation. Older age ($p<0.001$) and method of diagnosis ($p<0.001$) were independently associated with increased likelihood of having an ER positive tumour. Hospital of diagnosis and deprivation lost their association with ER positivity (table 15).

Table 14: Univariate analysis of association between having an ER positive tumour and age at diagnosis, deprivation and method and hospital of diagnosis (p value derived from χ^2 test)

		Early – No. ER positive (%)	Late – No. ER positive (%)
Age	<39	46(28.9)	102 (63.8)
	40-49	162 (38.8)	336 (72.4)
	50-64	471(49.6)	1296 (81.6)
	65-74	337(56.4)	475 (81.3)
	75+	172(57.7)	262 (82.1)
	p	*<0.0001**	*<0.0001**
Deprivation	1	231 (53.5)	467 (81.4)
	2	421 (48.5)	1235 (79.7)
	3	464 (49.8)	769 (77.6)
	p	*0.252*	*0.18*
How Diagnosed	Symptomatic		1497 (75.6)
	Screen detected		974 (85.7)
	p		*<0.001*
Hospital	1	192 (46.5)	405 (76.1)
	2	403 (50.6)	1127 (82.0)
	3	163 (50.8)	195 (76.8)
	4	320 (51.5)	744 (77.9)
	p	*0.425*	*0.009**

***Statistically significant**

Table 15: Multivariate analysis of association between having an ER positive tumour and age at diagnosis, hospital of diagnosis, deprivation and method of diagnosis.

		Relative risk of ER positive tumour (95% confidence interval)	P value
Year	1980-1989	1	<0.0001
	1996-2001	3.22 (2.81 to 3.69)	
Age	<39	1	<0.0001
	40-49	1.49 (1.14 to 1.97)	
	50-64	2.06 (1.39 to 2.67)	
	65-74	2.71(2.06 to 3.55)	
	75+	2.97 (2.19 to 4.00)	
Hospital			0.22
Deprivation			0.126
Method of diagnosis	Symptomatic	1	<0.0001
	Screen detected	1.81 (1.46 to 2.26)	

Discussion

This data shows that there has been an increase in the proportion of hormone sensitive breast cancer between the two time periods, from 50.1% to 79.3%. The increase in ER positive tumours occurred in all deprivation categories and there was a trend for more ER positive tumours in the most affluent group, however, this was not significant in either of the time periods. There was an increase in the proportion of ER positive tumours in all of the age groups, but the increase was particularly marked in those patients under 65. Screen detected tumours were more likely to be ER positive, and there was no significant association between hospital of diagnosis and ER status. The increase in percentage of ER positive tumours over time was independent of age, deprivation, breast screening or the hospital of diagnosis. Age was independently predictive of having an ER positive tumour regardless of how ER status was determined.

The rate of 79.3% ER positive tumours in 1996-2001 is similar to that of Li *et al.* (154), who found a rate of 75.4 in 1992 and 77.5 in 1998. However, in the early time period the proportion of ER positive tumours was only 50.1% which is significantly lower. Thomson et al demonstrated an ER positivity rate of 61.2% for patients diagnosed from 1980 onwards who had ER status determined by LBA. They used a similar cut of 20 fmol as determining ER positivity (168). Alberts et al found a rate of 57% ER positive tumours for node positive patients who had ER determined by LBA (169). While the rate demonstrated here of 50.1% in the early cohort is significantly lower than the later cohort it is largely similar to groups of patients diagnosed at a similar time. The reason for this dramatic increase in ER positive breast cancer may be methodological because two different types of assay were used in the study or there has genuinely been an increase in ER positive breast cancer.

The obvious shortcoming of this study is that two different types of assay were used. Concordance between the two techniques has variously been suggested to be around 80-90% (164;165). LBA tends to underestimate ER positivity, especially in those tumours that are weakly positive for ER by IHC (169). In addition, LBA tends to underestimate ER positivity in pre-menopausal women because IHC detects

oestrogen bound receptors while LBA using short term incubation cannot (169). However, with the longer incubation time of 24 hours used in this LBA, endogenous oestrogen is displaced by the radioactive ligand so this effect should be minimal (166). Taking these factors into account we would expect the increase in proportion of ER positive tumours to be smaller than the 30.3% we observed. Thus, methodological differences do not explain all of the increase.

Although concordance between LBA and IHC has been suggested to be 80-90% (164). The discordance is minimised by using a cut off of 20 fmol/mg protein rather than 10 fmol/mgprotein (170), however, it is difficult to predict which of our results would be discordant. Comparison of these results with the results of previous studies might give some assessment of the expected magnitude of discordance that might be observed if the tumours from the early time period were re-stained using IHC (table 16). All of these studies measured ER status using LBA and IHC on the same tumours samples.

Table 16: The relative change in ER status seen in previous studies

Study	Harvey *et al*(171)	Alberts *et al*(169)	Thomson *et al* (168)	Stierer *et al*(172)
% ER positive by LBA	78.9	57	61.2	76.2
% ER positive by IHC	70.5	55	70.2	81.2
% Absolute change in ER positive tumours	-8.4	-2	+9	+5
% Relative change in ER positive tumours	-40	-5	+23	+21

It is clear from these results that the effect of differences in methodology would not account for all of the increase in ER positive breast cancer we have observed. At worst it would account for a 23% increase in ER positive breast cancer in moving from LBA to IHC (168). We must therefore be seeing a genuine change in the prevalence of hormone sensitive breast cancer of at least 7 %, although it could be higher.

A further shortcoming of this study is the differences between the two populations. There were significantly more women in the age group 50-64 in the later cohort. In

addition, there were more women in the intermediate and affluent women in the later cohort. There were also significant differences in the tumour pathology. There were more small, node negative tumours in the later cohort, although pathological data was not available for a significant proportion of the early cohort of patients. These differences are largely attributable to the introduction of breast screening in the intervening period. This meant that more patients were diagnosed with breast cancer in the 50-64 age group. In addition, deprived women are less likely to attend for breast screening (data from Scottish Breast Screening Unit), so deprived patients are relatively under represented. Furthermore, between the census of 1981 and 2001 the population of Scotland became more affluent (16). Patients diagnosed at breast screening are more likely to have smaller, node negative tumours because they should be picked up at an earlier stage. Despite these differences, the increase in ER positive tumours between the early and late cohorts was independent of age or deprivation, so these factors had a minimal effect.

Apart from the methodological difficulties there may well have been an overall increase in ER positive breast cancer. There has not, however, been a different rate of increase for each of the deprivation categories which might explain why affluent women have previously been observed to have a better outcome from breast cancer. It has previously been shown that affluent women are more likely to have ER positive breast cancer (10). In agreement with this finding, this study has demonstrated a significantly greater proportion of ER positive breast cancer in the affluent group when considering both groups of patients together, but this was not true when each cohort of patients were considered separately. Therefore the increase in ER positive breast cancer which has been observed overall has occurred for all deprivation categories and any change in aetiological factors must be true for everyone and not just the more affluent patients.

Not only do ER positive and ER negative breast cancer behave differently in response to hormone manipulation (133), but recent studies have identified distinct patterns of relapse for ER positive and ER negative cancer, which has suggested that they are two different diseases (173). ER negative breast cancer tends to relapse early within the first two years of follow up and there is a difference in survival compared with ER positive breast cancer, however, with longer term follow up this

difference appears to diminish (173). This has lead to the observation that the aetiologies of the two types of breast cancer are distinct (174).

It has long been established that older age is associated with an increased incidence of ER positive breast cancer(157). These results show that regardless of how ER status is measured this relationship remains. There was a significant change in the age distribution between the two cohorts of patients examined, which was due to the introduction of breast screening, and this may have confounded the results by giving a lead time bias. Breast screening is more likely to pick up the slower growing tumours, ER positive tumours and its introduction in between the two cohorts examined here may have increased the number of ER positive tumours that were diagnosed. However, there was a general increase in the proportion of ER positive tumours across all age groups, which suggests that while breast screening undoubtedly had an affect, other factors must also have been responsible.

ER positive breast cancer is associated with early menarche and nulliparity (175;176), however, this appears to be more important in post-menopausal breast cancer than premenopausal breast cancer (156;162). Patterns of fertility have changed over time, with more nulliparous women and most women having a later age at first pregnancy and women having an earlier menarche (4). Improvements in socio-economic status mean that women tend to have their first pregnancy later and tend to be nulliparous. In addition, childhood malnourishment is associated with later menarche and early menopause(177), so improvements in nutrition overall should result in earlier menarche. Changes in these reproductive factors may therefore have contributed to an increase in ER positive breast cancer, however, as they are all associated with socio-economic status one might expect to see a difference in incidence of ER positive breast cancer between the deprivation categories. This suggests that either these factors only make a small contribution to the likelihood of having an ER positive breast tumour or the difference in these reproductive factors between deprivation categories is small.

HRT use is associated with increased breast cancer risk (27). Its use has rapidly increased since its introduction in the 80's (22). Studies have also shown that HRT use is particularly associated with ER positive breast cancer (178;179). Therefore,

increases in HRT use may also be responsible for the increase in ER positive breast cancer seen in this study. HRT use is also associated with affluence(28) and improvements in affluence overall might account for increases in HRT use and by extension ER positive breast cancer. The difference in proportion of ER positive breast cancer between the deprivation categories in this study was modest and may have been contributed to by differences in the use of HRT but it is more likely that there has been an overall increase in uptake.

The incidence of obesity has increased over time (180). The association of obesity and risk of ER positive breast cancer is somewhat complicated. In pre-menopausal breast cancer obesity appears to be protective for risk of ER positive breast cancer (162). Conversely, in postmenopausal women it appears to increase the risk (161). Increased levels of physical activity in younger and older women appears to reduce the risk of both ER positive and ER negative breast cancer (161). Post menopausal obesity is associated with higher levels of endogenous oestrogen and this is thought to be the reason why obesity is associated with increased postmenopausal cancer risk (161). In premenopausal women, obesity is associated with menstrual irregularities resulting in lower circulating oestrogen and lower breast cancer risk (162). It would therefore be expected that increasing obesity in the population as a whole would cause a rise in ER positive postmenopausal but not premenopausal breast cancer but these results have shown that ER positive breast cancer has increased for all age groups.

ER negative breast cancer has previously been shown to be associated with socio-economic deprivation in Scotland (10). In addition, a study from California showed that the difference in incidence of ER positive breast cancer is independent of ethnic group or age (176). These results show that there is an excess of ER negative tumours in deprived patients when both cohorts were considered together, but this association did not remain on multivariate analysis or when each cohort was considered individually. The aetiological factors for hormone sensitive breast cancer discussed above tend to be more prevalent in affluent women. They tend to have an earlier age at menarche, are more likely to be nulliparous or have a later age at first birth and they are more likely to take HRT. The incidence of these factors has increased more in affluent women than deprived women so it would be expected that

the increase in ER positive breast cancer would be more marked in affluent women but this was not the case. The reason this was not identified may be due to inadequate numbers. However, the results from chapter 1 have suggested that a survival gap no longer exists and the incidence of risk factors may have increased for the whole population.

Conclusion

There appears to have been a genuine increase in the proportion of ER positive breast cancer over time. Differences in the technique of determining ER status may account for some of the difference but they do not explain all of it. Changes in hormonal factors that have been implicated in the aetiology of ER positive breast cancer and the increasing use of HRT over the last 20-30 years may have led to more ER positive breast cancer. Although these aetiological factors are more prevalent in affluent women, the increase in ER positive breast cancer was seen in all deprivation categories and all age groups. This suggests that there have been global changes in aetiological factors which have increased the proportion of ER positive breast cancer but would not account for the increase in incidence in affluent groups.

The reasons for the increase in ER positive breast cancer are probably multifactoral. Increasing use of HRT has probably increased the incidence of postmenopausal breast cancer. In addition, the introduction of breast screening has resulted in the detection of more slow growing tumours which tend to be ER positive. Increases in premenopausal breast cancer are partly due to improvements in nutrition resulting in earlier menarche as well a general improvement in affluence for the whole population has led to the increasing incidence of nulliparity and later age of first birth.

Alternatively there may be an as yet unidentified endogenous biological change occurring within breast cancer cells themselves, which is resulting in the development of more ER positive breast cancer. Understanding the shifting pattern of hormone sensitive of breast cancer is important for determining adjuvant therapy for breast cancer.

Chapter 4

Deprivation and the systemic inflammatory response to breast cancer.

Introduction

Thus far, pathological features of the tumour have been examined as potential reasons why deprived and affluent women should have different breast cancer outcomes. Traditionally, prognosis in breast cancer has been determined by pathological characteristics of the tumour and axillary nodes using the Nottingham prognostic index or TNM stage. In addition, the oestrogen and HER-2 receptor status of the tumour specimen are routinely measured to guide adjuvant therapy. The preceding chapters have shown that while some of these factors might explain the deprivation gap, they do not account for the differences that have previously been observed, which leaves the question of what other factors might be involved.

Pathological factors do not provide clear distinction between patients who will go on to develop recurrence and die of their disease. There is, therefore, continuing interest in evaluating factors which will improve the prediction of outcome. To date, serum markers of prognosis have had limited usefulness and have not been put into routine clinical use.

It is increasingly recognised that it is not only the intrinsic properties of tumour cells themselves which determine tumour spread, but also the host inflammatory response (181;182). Indeed, the systemic inflammatory response, as evidenced by elevated circulating concentrations of C-reactive protein, has been shown to be a disease independent prognostic factor in a variety of operable tumours (183-187). In particular, an elevated C-reactive protein, measured either prior to or following curative surgery, has been shown to predict recurrence and overall survival, independent of stage, in patients with primary operable colorectal (96) pancreatic (183) and bladder cancer (185).

There have only been a few studies which have examined the prognostic role of C-reactive protein concentration or its primary mediator interleukin-6 in breast cancer (102;112;114-116;118;188). These studies described a raised systemic inflammatory response in metastatic and locally advanced breast cancer. However, to date the relationship between C-reactive protein, Il-6 and outcome has not been examined in women with primary operable breast cancer.

A raised C-reactive protein is also known to exist in patients from more deprived socio-economic backgrounds. Part of this increase appears to be due to increased prevalence of smoking and increased BMI. However, there also appears to be a raised "inflammatory state" which exists in people of lower socio-economic status (94;95). People of lower socio-economic status have CRP levels that are within the reference range for the population but below that which is clinically significant, and this appears to predispose them to coronary heart disease and diabetes (189).

Whether a raised background CRP predisposes to poor outcome in cancer is not clear. A recent study in colo-rectal cancer showed that people of lower socio-economic backgrounds had worse overall and cancer specific survival. In addition, it appeared in these patients that the presence of a systemic inflammatory response in the more deprived patients accounted for the differences in survival (96). In patients with primary breast cancer it has been shown that deprived women have a raised systemic inflammatory response which is independent of tumour pathology (120). This therefore poses the question of whether socio-economic differences in outcome from breast cancer might be attributable to a raised background inflammatory response. If there is a raised inflammatory response to cancer, is this due to a raised background response to other inflammatory co-morbidities or is it due to an excessive and inappropriate response to the primary tumour itself?

The first aim of this chapter is to examine if socioeconomic differences in inflammatory response to primary breast cancer exist pre or post operatively. Differences in pre-operative systemic inflammatory response would reflect the host response to the tumour itself and differences in the post-operative response would reflect background inflammation. The second aim is to assess whether the pre or

post operative systemic inflammatory response predict survival and if they might account for socio-economic differences in outcome.

Methods

Patients

Patients undergoing surgery for primary operable breast cancer in Glasgow Royal Infirmary and Western infirmary Glasgow were recruited for this study between October 2000 and January 2002. Each patient was approached pre-operatively, counselled about the study and asked to sign a consent form.

Each patient had a sample of venous blood taken in an EDTA tube. A second sample of blood was then obtained approximately 12 months later. All samples were centrifuged at 1000 x g for fifteen minutes then serum was stored at -20°C for subsequent analysis

Demographic data were also collected for each patient, including age, smoking status, and deprivation category (measured using Carstairs scores). The pathological data was also recorded for each patient. Including tumour size (measured in millimetres), lymph node involvement and histological grade. These were combined and expressed as the Nottingham prognostic index, which was further categorised into good prognosis (NPI $\leq$ 3.4), intermediate prognosis (NPI >3.4 $\leq$5.4) and poor prognosis (NPI > 5.4). The ER status and HER-2 status were also recorded. Those patients who had greater than 10% positive staining on IHC for oestrogen receptors were considered positive. The patients who were 3+ positive on IHC for HER2 were considered positive. Those patients who were 2+positive on IHC for HER2 had FISH testing. Those that amplified on FISH were also considered HER2 positive as well.

The nature of adjuvant treatment was recorded for each patient. Including whether they underwent radiotherapy or chemotherapy and if they had hormonal therapy, this was mainly in the form of tamoxifen.

All patients were then followed up until 31st July 2005 for recurrence or death. Initially the death register was searched for those patients who were deceased and their cause of death. Case notes were reviewed for all patients to identify if there

had been further deaths not recorded in the death registry. Those patients (of whom there were 4) whose case notes could not be obtained and who were not registered as deceased in the death register were assumed to be fit and well with no recurrence of their disease.

Biochemical Analysis

C-reactive protein

C-reactive protein was determined using a Tina-quant® C-reactive protein (latex) high sensitive assay (Roche Diagnostics, Indianapolis, IN). The serum sample was mixed with a buffer (Tris(hydroxymethyl)-aminomethane 16 mmol/L, pH 7.4) this was then added to the reagent (latex particles coated with anti-CRP mouse monoclonal antibodies). The reagent then reacts with antigen in the sample to form an antigen/antibody complex which is then measured turbidimetrically using a Roche/Hitachi 902 analyser (Roche Diagnostics, Indianapolis, IN).

The measuring range for the assay is 0.1-20 mg/L. For those C-reactive protein values above 20 mg/L the serum was diluted with 0.9% NaCl to give a value within the measuring range and the result multiplied by the dilution factor(190).

Those patients with a C-reactive protein greater than 10mg/L were considered to have a clinically significant inflammatory response.

Interleukin-6

Il-6 was measured using a quantitative sandwich enzyme immunoassay technique. The Quantikine® HS immunoassay kit (R+D Systems Europe, Abingdon) was used for measurement. This contained *E. coli*-expressed recombinant human IL-6, which is essentially added to each sample and forms an antibody-antigen complex with IL-6 present in each sample. A polyclonal antibody specific for IL-6 is then added. The reaction is then amplified and a colour develops in each microplate. The development of the colour is stopped then the optical density is measured to determine the concentration of IL-6 in each sample.

The steps in the analysis are summarised in figure 15. Firstly 100µl of sample is added to each well of a microplate. Each well is pre-coated with mouse monoclonal

antibody against IL-6. 100uL of assay diluent (a buffered protein base with preservatives) is then added to each plate. The microplate is then incubated for 2 hours at room temperature on a horizontal orbital microplate shaker. The wells were then washed with a wash buffer 6 times. 200 μL of Il-6 conjugate (the polyclonal antibody against IL-6) was then added to each well and the microplate incubated for 2 hours on the microplate shaker. The microplate was then washed six further times with the wash buffer. 50μL of substrate solution were then added to each well and the plate incubated for a further 60 minutes at room temperature. 50 μL of amplifier solution were then added to each well and the solution left to incubate for a further 30 minutes. Following addition of the amplifier colour began to develop then 50 μL of a stop solution was added to each well.

The microplates were then read (within 30 minutes) using a Multiska Ascent Plate Reader and associated software (Thermo Life Sciences, Basingstoke). The reader was set to 490nm optical density and the optical density of each sample was measured. The concentration of IL-6 was determined by first finding the absorbance value on the y-axis, extending a line to the standard curve and determining the x coordinate of the point of transaction (see figure 16), this gives the concentration of Il-6 in pg/mL.

Those patients with an Il-6 concentration than 5pg/mL were considered to have a clinically significant inflammatory response.

Scoring

A "CRP score" and an "Il-6 score" were calculated for each subject. A score of one was given for a CRP greater than 10 either pre or post operatively. A score of one n was also given for an IL-6 concentration over 5pg/mL either pre or post operatively. This meant that each subject scored 0, 1 or 2 for their CRP score and their Il-6 score (table 17)

Statistical Analysis

All data was entered onto SPSS for Windows version 9 (SPSS, Chicago, IL) for statistical analysis. Mean CRP concentration was compared for various groups of

patients to assess if CRP was related to demographic, treatment or pathological factors using a t test or ANOVA (where more than two groups were being compared). The relationship between clinicopathological factors as well as pre and post operative CRP and IL-6 and survival was determined using cox regression analysis for both the univariate and multivariate analysis. In addition, log rank testing was used to give a crude estimate of the relationship of CRP score with survival a Kaplan Meier curve was plotted. CRP score was then subjected to Cox regression analysis as well P values less than 0.05 were considered statistically significant.

Ethical Approval

Ethical approval for the study was obtained from the local research ethics committee.

ASSAY PROCEDURE SUMMARY

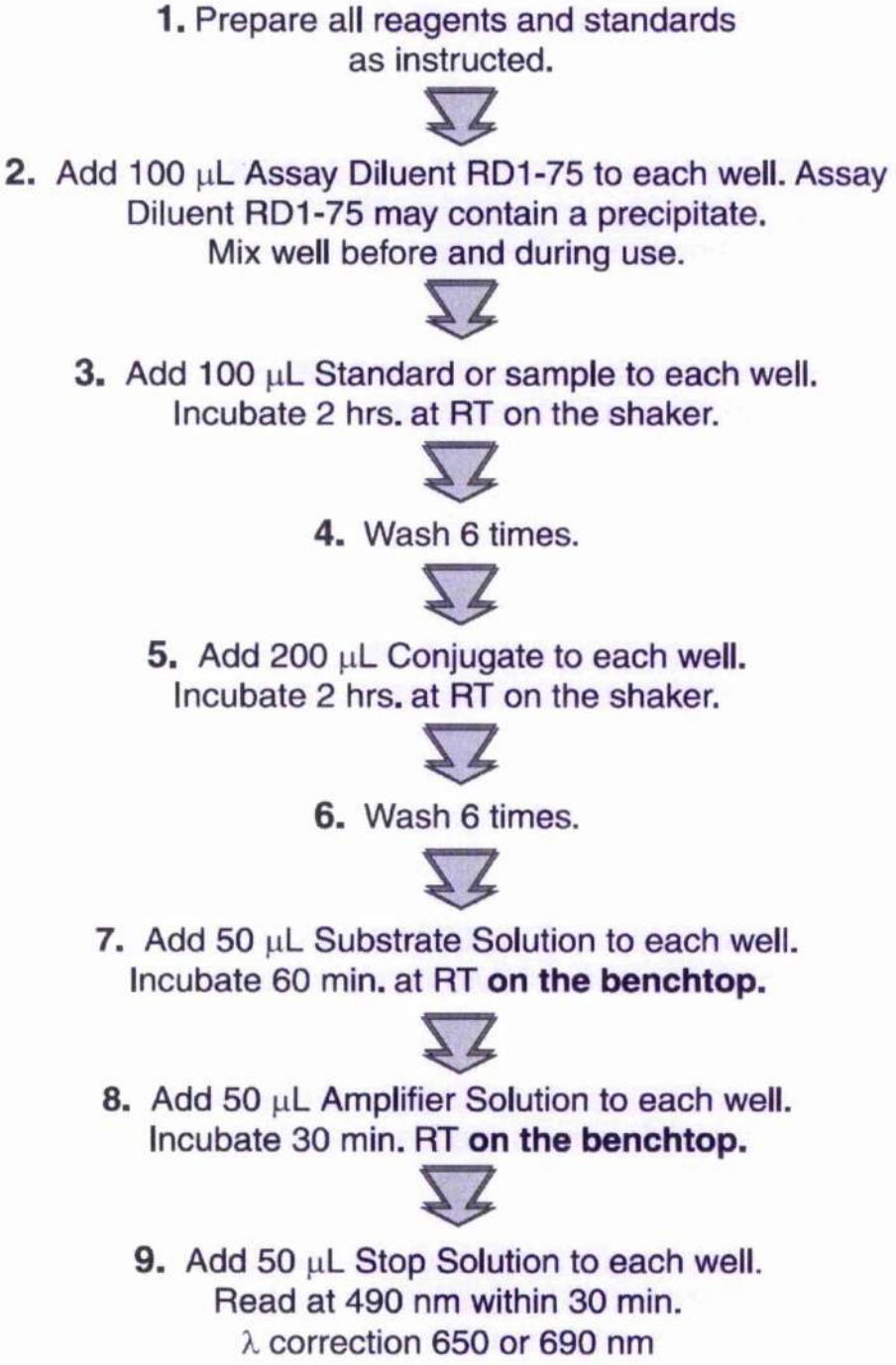
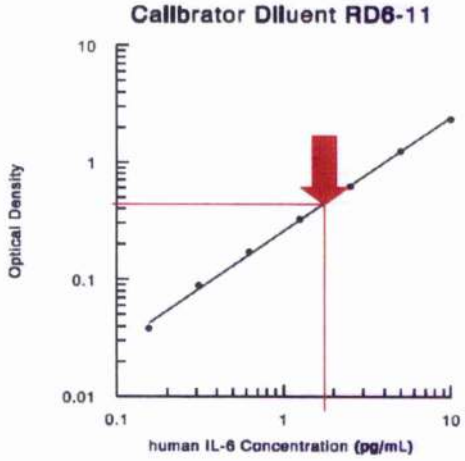


Fig 15: Summary of procedure for IL-6 measurement (191)



pg/mL	O.D.	Average	Corrected
0	0.130 0.134	0.132	—
0.156	0.166 0.173	0.170	0.038
0.312	0.218 0.223	0.221	0.089
0.625	0.296 0.311	0.304	0.172
1.25	0.447 0.469	0.458	0.326
2.5	0.731 0.773	0.752	0.620
5	1.348 1.401	1.375	1.243
10	2.389 2.566	2.478	2.346

Fig 16: Calibration curve for calibrator diluent to illustrate how to measure IL-6 concentration

Table 17: Calculation of CRP and Il-6 score. Possible scores 0,1 or 2.

Pre-operative	**Score**	**Post-operative**	**Score**
CRP $\leq$10mg/l	0	CRP $\leq$10mg/l	0
CRP >10mg/l	1	CRP >10mg/l	1
Il-6 $\leq$5ng/l	0	Il-6 $\leq$5ng/l	0
Il-6 >5ng/l	1	Il-6 >5ng/l	1

Results

In total 194 patients were recruited for the study. 11 were excluded as they were found to have metastases at presentation; had palliative resection or were found to have a second non-breast primary at diagnosis. 183 patients were therefore included in the study, 81 patients from hospital 1 and 102 from hospital 2. 154 patients had a second blood sample taken post operatively at approximately 12 months. 4 of the remaining patients had died in the intervening period and the remainder did not have a blood sample taken (25 patients).

The demographics of the patients are shown in table 18. The majority of patients were over 50 (86.9%), non smokers (67.8%) and of intermediate deprivation category (48.6%).

Table 18: Demographic characteristics of the patients

	Number of Patients	Percentage of patients
Age		
<50	24	13.1
>50	159	86.9
Smoker	49	27.7
Non-smoker	124	67.8
Unknown	10	5.5
Deprivation category		
Affluent	21	11.5
Intermediate	89	48.6
Deprived	73	39.9
Hospital of Treatment		
1	81	44.3
2	102	55.7

The pathological data for the patients is as shown in table 19. The majority of patients had intermediate prognosis tumours (49%) that were ER positive (80%) and HER2 negative (77%). The adjuvant treatment the patients received is shown in table 20. of the study population, 39% had chemotherapy, 64% had radiotherapy and 81% had tamoxifen

Table 19: Pathological characteristics of the patients

	Patients(%) n=183
Tumour size	
≤2cm	114 (63)
>2cm	69 (37)
Grade	
I	40 (22)
II	60 (33)
III	83 (45)
Involved lymph node	
0	104 (57)
1-3	49 (27)
>3	30 (16)
NPI	
Good (<3.4)	61 (33)
Intermediate (3.41– 5.4)	89 (49)
Poor (>5.4)	33 (18)
Oestrogen receptor status	
Negative	37 (20)
Positive	146 (80)
HER2 status	
Positive	18 (10)
Negative	141 (77)
Unknown	*24 (13)*

Table 20: Adjuvant treatment received by the study population

Adjuvant treatment	Number of patients (%)
Chemotherapy	
Yes	72 (39)
No	92 (50)
Unknown	19 (11)
Radiotherapy	
Yes	117 (64)
No	48 (26)
Unknown	18 (10)
Hormonal therapy	
Yes	148 (81)
No	35 (19)

At follow up on 31st July, 2005, 19 patients had died of breast cancer and 11 of intercurrent disease. A further 6 patients had had local recurrence which had been successfully treated by resection. The median follow up was 53 months (range 42.4 to 57.8 months).

On measuring pre-operative serum CRP the minority of patients (11%) had a clinically significant inflammatory response (CRP>10 mg/L). The same was true for Il-6. 11% of patients had a clinically significant Il-6. Similar findings were true of the post-operative CRP, 12% of patients had a clinically significant inflammatory response. 18% of patients had a clinically significant Il-6 post-operatively (see table 21).

Table 21: Pre op CRP (mg/l) and IL-6 (pg/l) results (n =183) and post op results (n=154)

	Number of patients
Pre op CRP (n = 183)	
<10 mg/l	162 (89)
≥10 mg/l	21 (11)
median (range)	2.28 (0.10-22.78)
Pre op IL-6 (n = 183)	
<5 pg/l	163 (89)
≥5 pg/l	20 (11)
median (range)	2.08 (0.50-25.08)
Post op CRP (n = 154)	
≤10 mg/l	134 (88)
>10 mg/l	19 (12)
median (range)	2.40 (0.1 – 93.5)
Post-op IL-6 (n = 154)	
≤5 pg/l	125 (82)
>5 pg/l	28 (18)
median (range)	2.4 (0.4-25.8)

On calculating the CRP score, the majority of patients scored 0 (80%), 16% of patients scored 1, and 4 % scored 2. The majority of patients had an Il-6 score of 0 (80%), 14% scored 1 and 5% scored 2 (see table 22).

Table 22: CRP and IL-6 scores (n=154)

	No. patients (%)
CRP Score	
0	122 (80)
1	25 (16)
2	6 (4)
IL-6 Score	
0	122 (80)
1	21 (14)
2	10 (6)

On t testing (and ANOVA for more than two comparisons), mean pre or post operative CRP was not related to age, deprivation category or smoking status. Pre-operative CRP had no statistically significant relationship to Nottingham prognostic index, ER status or HER 2 status. Post - operative CRP had no relationship to whether the patients had postoperative radiotherapy or chemotherapy or the HER2 status of their tumours. However, mean post-operative CRP was significantly greater in patients with a high NPI compared with those with intermediate or low NPI (22.8 compared with 7.03 and 5.53 respectively; p=0.012). Post-operative CRP was also significantly greater in patients with ER negative tumours (p=0.001) (table 23). Pre and post operative IL-6 was not related to age, deprivation, smoking, NPI, ER, HER2 or adjuvant therapy (table 24).

Table 23: Comparison of serum CRP with clinicopathological characteristics of the study group

Variable	Mean pre op CRP	p	Mean post op CRP	P
Age				
<55	3.22	0.075	5.43	0.87
>55	4.45		5.73	
Deprivation†				
Affluent	3.34	0.24	3.08	0.32
Intermediate	3.86		6.94	
Deprived	4.40		4.79	
Smoking				
Yes	3.80	0.41	4.84	0.26
No	5.41		6.79	
NPI†				
Good	3.95	0.75	5.53	0.012*
Intermediate	4.23		7.03	
Poor	3.56		22.82	
ER status				
Positive	3.88	0.41	4.07	0.001*
Negative	4.56		11.35	
HER2 status				
Positive	2.74	0.22	2.58	0.23
Negative	4.09		6.42	
Tamoxifen				0.004*
Yes	N/A		4.54	
No			9.95	
Chemotherapy				
Yes	N/A		4.57	0.11
No			7.83	
Radiotherapy				
Yes	N/A		5.32	0.73
No			6.07	

T test to compare mean CRP between groups. †ANOVA to compare mean CRP between groups.

* Statistically significant

Table 24: Comparison of serum IL-6 with clinicopathological characteristics of the study group

Variable	Mean pre op IL-6	p	Mean post op IL-6	P
Age				
<55	2.49	0.07	3.72	0.22
>55	3.36		4.82	
Deprivation†				
Affluent	1.84	0.12	3.06	0.11
Intermediate	3.04		4.63	
Deprived	3.43		4.61	
Smoking				
Yes	3.10	0.85	4.21	0.52
No	3.21		4.86	
NPI†				
Good	2.92	0.14	4.45	0.14
Intermediate	2.79		3.74	
Poor	4.01		6.30	
ER status				
Positive	2.93	0.28	4.39	0.86
Negative	3.55		4.57	
HER2 status				
Positive	2.30	0.28	4.61	0.21
Negative	3.14		2.84	
Tamoxifen				0.703
Yes			4.36	
No			4.73	
Chemotherapy				
Yes			3.60	0.33
No			4.40	
Radiotherapy				
Yes			4.10	0.71
No			4.45	

T test to compare mean IL-6 between groups. †ANOVA to compare mean CRP between groups.

On univariate analysis of patients who had had a pre-operative blood sample taken, NPI ($p<0.001$), ER status ($p=0.012$), HER2 status ($p=0.035$) and pre operative CRP ($p=0.044$) were significantly related to survival (table 25). However, on multivariate analysis only NPI ($p<0.001$) and pre operative CRP ($p=0.03$) were significantly predictive of survival (table 26)

Table 25: Univariate Cox regression survival analysis of pre operative CRP and IL-6 only (n=183)

	p	HR	95% CI
Age	0.07	1.03	0.69 - 2.10
Smoking	0.16	1.78	0.10 1.07
Deprivation (affluent/ intermediate/ deprived)	0.52	1.20	0.79 – 4.02
NPI (good/intermed/poor)	<0.001*	5.60	3.04-10.31
ER (pos/neg)	0.012*	0.39	0.18-0.81
HER-2 (pos/neg)	0.035*	2.68	1.07-6.72
Serum pre operative CRP	0.044*	1.07	1.00- 1.14
Serum pre operative Il-6	0.079	1.07	0.99-1.15

Table 26: Multivariate Cox regression survival analysis of pre-operative CRP and IL-6 (n=183)

	p	HR	95% CI
NPI (good/intermed/poor)	<0.001*	5.69	2.68 – 12.09
ER (pos/neg)	0.21	0.59	0.26 – 1.34
HER-2 (pos/neg)	0.72	1.19	0.46 – 3.11
Serum pre operative CRP (CRP<10/ CRP ≥10)	0.03*	3.78	1.18 – 12.15

On univariate analysis of patients who had had both a pre and post-operative blood sample taken again NPI (p<0.001), ER (p=0.012), HER2 (p=0.035) and preoperative CRP (p=0.044) predicted survival, however so did post-operative IL-6 (p=0.04)(table 27). On multivariate analysis of these patients, only NPI (p<0.001) and pre-operative CRP (p=0.04) predicted survival (table 28).

Table 27: Univariate Cox regression survival analysis including post operative CRP and IL-6 (n – 153)

	P	HR	95% CI
NPI (good/intermed/poor)	<0.001*	5.60	3.04-10.31
ER (pos/neg)	0.012*	0.39	0.18-0.81
HER-2 (pos/neg)	0.035*	2.68	1.07-6.72
Serum pre operative CRP	0.044*	1.07	1.00- 1.14
Serum pre operative Il-6	0.079	1.07	0.99-1.15
Serum post operative CRP	0.22	1.97	0.67 – 5.8
Serum post operative Il-6	0.04*	2.86	1.06-7.71

Table 28: Multivariate Cox regression survival analysis including post operative results

	P	HR	95% CI
NPI (good/intermed/poor)	<0.001*	5.41	2.34 – 12.51
ER (pos/neg)	0.53	0.74	0.29 - 1.89
HER-2 (pos/neg)	0.95	1.04	0.32 – 3.39
Serum pre operative CRP (CRP<10/ CRP ≥10)	0.04*	4.13	1.10 - 15.50
Serum post operative Il-6 (IL-6<5/ IL-6≥5)	0.38	1.70	0.52 – 5.55

When CRP and IL-6 were expressed as a score to examine the longitudinal relationship, log rank testing showed that CRP score predicted survival (p = 0.003 – table 29/ fig 17) but IL-6 score did not (p=0.171 – table 30/ fig 18).

Table 29: Cumulative survival vs CRP score

	1 year	2 year	3 year	4 year
CRP score = 0	1.0	0.975	0.934	0.902
CRP score = 1	1.0	0.880	0.840	0.800
CRP score =2	1.0	0.833	0.667	0.500

Log rank p=0.003

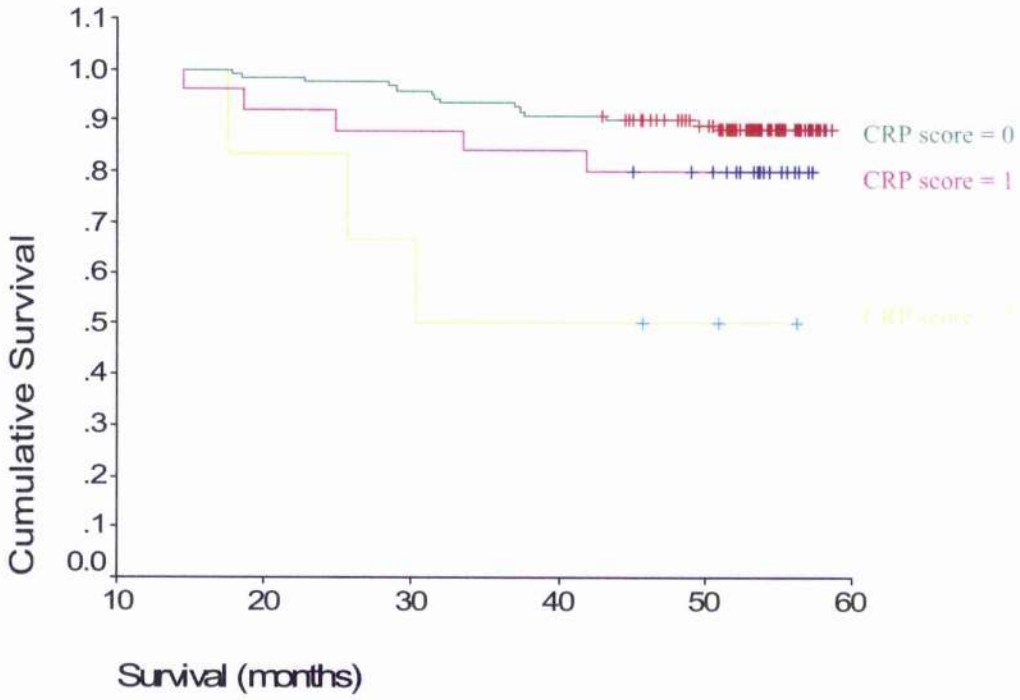


Fig 17: Kaplan Meier plot of CRP score vs survival

Table 30: Cumulative survival with Il-6 score

	1 year	2 year	3 year	4 year
IL-6 score = 0	1.0	0.975	0.934	0.893
IL-6 score = 1	1.0	0.905	0.810	0.810
IL-6 score =2	1.0	0.900	0.800	0.700

Log rank = 0.171

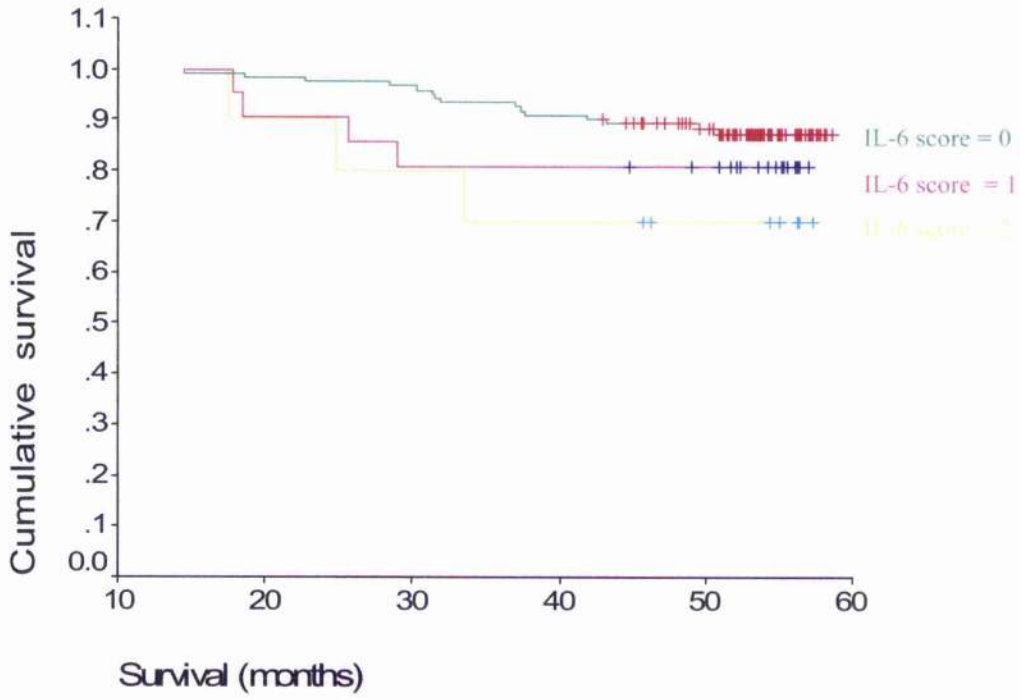


Fig 19: Kaplan Meier plot of survival and IL-6 score. Log rank 0.171

On Cox regression univariate analysis, survival was predicted by NPI ($p<0.001$), ER status ($p=0.018$) and CRP score ($p=0.004$) (table 31). While on multivariate analysis, only NPI ($p<0.001$) and CRP score ($p=0.001$) score predicted survival (table 32).

Table 31:Univariate Cox regression survival analysis of CRP score and survival

	P	**HR**	**95% CI**
NPI (good/intermed/poor)	<0.001*	4.97	2.52- 9.83
ER (pos/neg)	0.018*	0.37	0.16-0.87
HER-2 (pos/neg)			
CRP Score	0.004*	2.36	1.28-4.33
IL-6 Score	0.06	1.71	0.96 – 3.05

Table 32: Multivariate Cox regression survival analysis of CRP score and survival

	p	HR	95% CI
NPI (good/intermed/poor)	<0.001*	5.45	2.72-10.8
ER(pos/neg)	0.68	0.82	0.31-2.12
CRP Score	0.001*	2.69	1.47-4.91

Discussion

These results show that deprivation did not affect the magnitude of the systemic inflammatory response. Similar to the results in chapter 1, this data did not demonstrate a difference in breast cancer survival between deprived and affluent women. What has been shown, however, is that the pre-operative systemic inflammatory response (as measured by C-reactive protein but not by IL-6) did predict survival from breast cancer in this group of patients, independent of the established prognostic pathological factors: Nottingham prognostic index, oestrogen receptor or HER2 receptor status. The post-operative systemic inflammatory response did not appear to predict survival from breast cancer in these patients. A combination of the pre and post operative C-reactive protein to produce a C-reactive protein score was a significant predictor of survival in these patients, independent of their pathological or demographic characteristics.

The nature of the relationship between deprivation and the systemic inflammatory response is not clear. A difference in the background level of inflammation between affluent and deprived populations in an apparently "healthy" population has been shown in large epidemiological studies (94;95). After correction for smoking and obesity, both of these studies still demonstrated a raised CRP in deprived patients. It was therefore concluded that because CRP is associated with increased risk of cardiovascular events(119) that the presence of low grade inflammation in deprived groups explained their increase risk. In both of these large studies the difference was in the reference range for the normal population and below the level at which an inflammatory response would be considered significant (94;95). This suggests that any difference in the magnitude of the systemic inflammatory response between socio-economic groups is small. It is not therefore surprising that in this study with relatively small numbers that this study was unable to demonstrate a difference in CRP concentration between socio-economic groups independent of pathological factors. In agreement with the findings of chapter 1 but not, several large epidemiological studies(8;10;19;45;48;90), there was no significant difference in pathology or survival between socio-economic groups. Therefore, with the small numbers involved in this study it has been impossible to demonstrate that a

difference in systemic inflammatory response might account for survival differences between socio-economic groups. Clearly a larger study would be required for this.

A further confounding factor is the magnitude of the systemic inflammatory response. The majority of patients in this study did not have a clinically significant inflammatory response which further confounded the ability for the study to demonstrate any significant differences between socio-economic groups. In colorectal cancer a difference in the systemic inflammatory response between socio-economic groups has been suggested as a reason for survival differences (96). However, in colorectal cancer there is a more significant inflammatory response and its associated mortality is greater than breast cancer. In the study by McMillan et al (2003) although there were smaller numbers of patients with a shorter period of follow up there were enough events and a sufficient number of patients with an inflammatory response to show a difference between socio-economic groups. With longer follow up (for example 10 years), and therefore with more mortality, of the current group of patients with breast cancer it may be possible to show a difference between socio-economic groups without a further increase in numbers.

Despite this study not demonstrating a difference between socio-economic groups, it has shown that survival from breast cancer can be predicted by the pre-operative C-reactive protein but not the post operative C-reactive protein, independent of other pathological factors. However, combining the two to create a "CRP score" is a strong predictor of survival in breast cancer. Interleukin-6 was less successful at predicting survival than C-reactive protein.

The ability of the pre-operative systemic inflammatory response to predict survival in this group of patients with primary operable breast cancer confirms findings in colorectal, bladder, prostate, lung, lymphoma, pancreatic and gastric carcinomas. Although it has not been confirmed in primary breast cancer before, a raised systemic inflammatory response has been demonstrated in patients with metastatic (118) and locally advanced (116) breast cancer.

Contrary to previous studies, this study was unable to demonstrate a relationship between IL-6 and breast cancer survival. A raised post-operative IL-6 was

associated with survival on univariate analysis but the relationship lost its significance on multivariate analysis. Raised serum IL-6 has been shown to be associated with poor prognosis in patients with metastatic breast cancer and patients with locoregional disease (102;113-115) but has not previously been shown to be associated with survival in patients with primary operable breast cancer. In fact the relationship between survival, serum IL-6 and other types of cancer is somewhat inconsistent. Few studies have shown a raised IL-6 in patients with cancer even in those losing weight (101), who would be expected to have the greatest inflammatory response. It therefore appears that the majority of IL-6 produced in response to cancer is produced locally in the tissues and little of it spills over into the circulation. So it is not surprising that in the present study of patients with primary breast cancer that not only was Il-6 not raised, it was also unable to predict prognosis.

Post-operative C-reactive protein did not predict survival as was previously shown in colorectal cancer (192). However, the number of patients who had a post-operative C-reactive protein was smaller than those who had a pre-operative level measured so it may have been due to relatively small numbers that this relationship was not significant. In addition, the low mortality and relatively short follow up may also have contributed. A further study with larger numbers and longer follow up would be required.

While the pre-operative systemic inflammatory response but not the post-operative one should determine prognosis may simply be a function of the number of patients in the study, there may also be other reasons. The systemic inflammatory response is a reflection of the host response to the tumour rather than the malignant potential of the tumour itself. It is also a reflection of the background "stress response" of the patient even without the presence of a tumour, determined by the presence of pre-existing cardiovascular disease, obesity and smoking (94;95). The presence of the "background response" also appears to reflect cancer incidence but more importantly the likelihood of cancer mortality (193). The fact that the pre-operative but not the post-operative systemic inflammatory response was important suggests that it is the presence of a tumour that is more important in the genesis of this response rather than co-morbidity. However, this study did not include age and co-morbidity matched controls so no definite conclusion can be drawn on this. An alternative

explanation is that if the systemic inflammatory response is a reflection of the tumour load then a post-operative measurement should be able to detect the presence of micrometastases or sub-clinical disease. As this study has shown breast cancer does not induce a large systemic inflammatory response so the presence of sub-clinical disease or micrometastases would be unlikely to either.

Despite the inability of the post-operative C-reactive protein to predict survival, when it is combined with the preoperative C-reactive protein and expressed as a "CRP score" to examine the longitudinal relationship between C-reactive protein and survival, the "CRP score" is a strong predictor of survival. The reasons for this are not clear. By examining the longitudinal relationship a measure is obtained of the host response to the tumour but also the background "inflamed state" of the subject. Chronic inflammation is thought to promote carcinogenesis. A study of background level of inflammatory markers (including C - reactive protein) in healthy subjects showed that a raised C-reactive protein was associated with an increased risk of cancer incidence and also of cancer death (193). The patients with both a pre and post-operative systemic inflammatory response therefore receive a "double hit." Firstly, they already have a raised background inflammatory response but they are also mounting a raised systemic inflammatory response to their tumour. This may result in worse survival.

The "double hit" might also explain why deprived patients have a worse outcome from breast cancer than affluent women. Although it has not been demonstrated with this data, deprived patients may have a raised background systemic inflammatory response due to increased BMI, smoking and cardiovascular co-morbidity. They then develop a cancer and therefore in addition to the systemic inflammatory response to the tumour they are also in a more "inflamed state" and this gives rise to a poorer prognosis. Due to the small number involved in this study and the small number of events this process has not been demonstrated here and a larger study would need to be conducted to show this effect.

There are, however, several other possible explanations for why the CRP score should be a strong predictor of survival. It may be due to the initial response to the tumour being of sufficient magnitude pre-operatively that is maintained after the

tumour has been removed and all adjuvant therapy has been completed. A further explanation is that the presence of an inflammatory response post-operatively is due to the continued presence of malignant cells, either in the form of micrometastases or sub-clinical disease. Whatever the reason for a continued inflammatory response post-operatively, the result is an increase in the host metabolic rate leading to cancer associated malnutrition, cachexia and eventually death.

The cellular mechanisms behind the relationship between C-reactive protein and breast cancer survival are not clear. Tumour growth and metastasis is a complex process which involves mechanisms at the site of the tumour and distant to the tumour. The cytokines, including IL-6, released by the tumour itself as well as the surrounding tissues cause local tissue damage and tumour necrosis. These also spill over into the circulation to act on the liver to produce the acute phase reactants, one of which is C-reactive protein. While some of these effects are beneficial in initiating a host immune response to the tumour and limiting tumour growth, they can also be detrimental because an enhanced inflammatory response can actually promote tumour growth and metastasis.

In breast cancer, the presence of a large lymphocytic infiltrate into the tumour increases the likelihood of local recurrence(194) and confers a poor prognosis. This suggests that the resulting systemic inflammatory response is due to production by the tissues at the site of injury rather than the tumour itself. A similar situation exists in renal cancer, where the presence of a large lymphocytic response results in a poor prognosis (111). This contrasts with colorectal (110) and gastro-oesophageal cancer (195) where a poor lymphocytic infiltrate is associated with a poor prognosis and a raised C-reactive protein. In gastrointestinal tumours the tumour itself must therefore be the source of the interleukins which induce then systemic inflammatory response. Indeed in the study by Canna et al (2005), a poor lymphocytic infiltrate was associated with a raised C-reactive protein.

Conclusions

This study has shown that, in this group of breast cancer patients, there is no association between socio-economic deprivation and the magnitude of the systemic inflammatory response. There was no difference in survival between deprivation categories. This study has, however, shown that the presence of a systemic inflammatory response predicts survival from breast cancer independent of known and established predictors of outcome. The presence of a systemic inflammatory response pre-operatively is more prognostic and a post-operative response. However, combining the pre and post operative response and expressing then as a score is a strong predictor of outcome.

Clearly the pathological factors are most important in determining outcome ad prognosis in patients with primary operable breast cancer. In addition, the oestrogen receptor and the HER2 receptor status are important in determining adjuvant therapy. However, the systemic inflammatory response could prove to be a useful adjunct to these established prognostic factors. While there is no suggestion that patients with a systemic inflammatory response should be excluded from having surgery, they might benefit from manipulation of the inflammatory response pre and/or post operatively with non-steroidal anti-inflammatory drug or the newer COX 2 inhibitors. If it could be shown in a larger study with longer follow up, that patients from more deprived socio-economic backgrounds did indeed have a larger systemic inflammatory response, then adjuvant treatment of this group of patients, who have a worse outcome from breast cancer, might help to redress the balance.

Chapter 5

Conclusions

The assumption prior to commencing this piece of work was that the greater Glasgow Audit database would confirm the findings in previous work that there exists a deprivation gap in outcome for women with primary breast cancer. Surprisingly this has not been shown. However, the studies on which this assumption was based are to some extent historical and are based on populations diagnosed prior to the establishment of breast screening and MDT working. The data presented here are for women diagnosed in the post-breast screening era who have been treated in the context of a multidisciplinary team. The fact that no deprivation gap has been demonstrated suggests that the introduction of these two changes may have helped to eliminate the effect of socio-economic factors on outcome.

What really highlights this effect is that although deprived women have worse pathology in terms of tumour size and nodal status, even on the univariate analysis without correcting for these factors, they still do not fare any worse than more affluent women. Treatment for breast cancer has evolved in recent times with the introduction of the specialist breast surgeon, less extensive surgery, the introduction of anthracycline based chemotherapy, the aromatase inhibitors and most recently herceptin. While all of these factors have no doubt contributed to improved outcome across the board, the way in which breast cancer services are delivered has also played a large part.

Breast cancer treatment used to vary widely between geographic regions, Health Authorities (in England) and Health Boards (in Scotland) had no doubt contributed to socio-economic disparities. However, the introduction of the multidisciplinary team has ensured that the developments in breast cancer are introduced more uniformly for all patients with specialists working across different regions. Therefore, all women benefit from better and optimal treatment of their breast cancer.

However, the findings of chapter 2 suggest that even being treated by a specialist breast surgeon does not necessarily mean that everyone is treated equally. The mastectomy rate in Glasgow is slightly above average for the UK as a whole, with deprived women being more likely to have a mastectomy than more affluent women. From the data, this appears to be a reflection of larger tumour size in deprived women and would suggest that this is entirely appropriate. The wide variation in mastectomy rate between hospitals is, however, cause for concern. Although broadly speaking women are being treated appropriately, variations between surgeons suggest that there is still a lack of consensus on the best treatment. Despite the extensive evidence of the efficacy of conservation surgery there still appears to be a reluctance to accept it as equivalent to mastectomy. The variation between hospitals may be due to patient choice but most of the populations served by the individual hospitals are relatively heterogeneous so it is more likely that variation is due to the surgeons' preferences. Mastectomy is now thought to be associated with excessive psychological co-morbidity so it is a matter of urgency that this is recognised and attempts are made to utilise conservation surgery in women in whom it is appropriate.

A further issue that has been highlighted from this analysis of the Greater Glasgow Audit Database is the poor attendance at screening for women from deprived socio-economic groups. This is a well recognised phenomenon, however, breast screening has been available since 1991 and it would be hoped that these socio-economic differences in uptake would have been ironed out. Women from deprived areas seem to be as likely to attend their GPs with breast cancer related problems and appear to have little in the way of delay in presentation however breast screening still appears to be in some way less acceptable. Further efforts need to be made to address this and raise public awareness of breast screening.

The rising incidence of breast cancer but falling mortality may be due to changes in treatment and delivery of healthcare, they may also be due to a change in the hormone sensitivity of breast cancer. Comparison of the data on ER status from the Greater Glasgow Audit database with a group of patients diagnosed in 10 years previously has shown that there has been an increase in the proportion of ER positive breast cancer. While there are significant methodological differences in the

estimation of ER status between the two cohorts of patients, these differences cannot be explained by methodology alone. Over a similar time period there have been changes in the hormone related aetiological factors behind ER positive breast cancer. HRT use has increased; more women are nulliparous and have a later age at first pregnancy.

Non-hormonal factors which might have an influence are the rise in obesity and the introduction of breast screening which tends to identify ER positive breast cancers. Although the incidence of these factors has increased for all women they have increased more in affluent women and might explain why affluent women have better outcome. The data presented here did not confirm that there has been a greater increase in affluent women than deprived women. This may be a function of inadequate sample sizes as combining the early and late cohorts of patients demonstrated a difference in ER status between different deprivation categories.

Although there may be differences in pathology or aetiology between socio-economic groups the underlying reason for differences in outcome may relate to the host response to the tumour. The data presented in chapter 4 demonstrated that the pre-operative systemic inflammatory response to breast cancer predicted survival. The post-operative systemic inflammatory response did not predict survival. The post-operative systemic inflammatory response is a surrogate for the background "inflamed state" of the patient. Combining the pre and post operative systemic inflammatory response as a score gave a significant predictor if survival independent of tumour pathology or demographic factors.

Deprived patients are known to have a raised "background" systemic inflammatory response compared to more affluent women due to a higher incidence of obesity, smoking and cardiovascular disease. Although there was no demonstrable difference in CRP scores between the deprivation categories (probably due to small numbers), the systemic inflammatory response could potentially be reason why deprived patients appear to have worse outcome from breast cancer. They already have a background raised inflammatory state, due to cardiovascular disease, smoking and obesity. They then develop a cancer which triggers an additional systemic

inflammatory response and it is the combination of the two rather than simply the response to the cancer alone that results in a poor outcome.

Although there are disparities between affluent and deprived women in terms of the breast tumours they develop and the treatment they receive, it does appear that despite this there no longer exists a significant deprivation gap between rich and poor. Whether this finding will be borne out with longer follow up is not clear, however, it does appear that improvements in the way that healthcare is delivered has had the greatest effect.

Abbreviations

ANOVA	Analysis of variance
ATAC	Arimidex, tamoxifen alone or in combination
BMI	Body mass index
C/EBPβ	CAAT/ enhancer-binding protein
CI	Confidence interval
CMF	Cyclophosphamide, methotrexate and fluorouracail
COX 2	Cyclo-oxygenase 2
CRP	C-reactive protein
DCIS	Ductal carcinoma-in-situ
Dep Cat	Deprivation category
EDTA	Ethylenediamine tetraacetic acid
EQA	External quality assessment
ER	Oestrogen receptor
FISH	Fluoroscopic in situ hybridisation
GGHB	Greater Glasgow Health Board
HER-2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRT	Hormone replacement therapy
IARC	International Agency for Research on Cancer
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
ISD	Information statistics division
JAK	Janus protein tyrosine kinase
LBA	Ligand binding assay
MCN	Managed clinical network
MDT	Multi-disciplinary team
NHSBSP	National Health Service Breast Screening Programme
NPI	Nottingham prognostic index
OR	Odds ratio
PR	Progesterone receptor
RNA	Ribonucleic acid
SEER	Surveillance epidemiology and end results
SPSS	Statistical package for the social sciences
STAT3	Signal transducer and activator of transcription 3
TGF	Transforming growth factor
TNF	Tumour necrosis factor
TNM	Tumour nodes metastasis
UICC	International Union Against Cancer
UK	United Kingdom
USA	United States of America

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