Social factors and the natural history of breast cancer

1. Year of diagnosis and tumour location
2. Socio-economic status and prognosis

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I confirm that this thesis was composed by me.

I acknowledge that the work reported was performed by me using clinical data of patients from the Edinburgh Breast Unit. Exceptions to this are the statistical analyses from which Kaplan-Meier curves were derived; these were carried out by Gill Kerr, Western General Hospital, Edinburgh. Certain of the follow-up detail was provided by Dr Wilma Jack, Edinburgh Breast Unit, Edinburgh.

This thesis has not been submitted in candidature for any other degree, postgraduate diploma or professional qualification.

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ABSTRACT

Breast cancer is the most common form of malignancy in Scottish women and its incidence appears to be increasing with time. It is therefore important to identify factors associated with risk and outcome. In this thesis two separate but interrelated social aspects of the natural history of breast cancer have been examined – (i) the location of the primary tumour within the breast in two groups of patients diagnosed 40 years apart and (ii) the effects of socioeconomic status on prognostic factors and outcome of patients with breast cancer. Whilst breast cancer occurs equally in right and left breasts, tumours most commonly affect the upper outer quadrant (UOQ) of the breast. However, there is no information as to whether the incidence has changed over time. To address this, the present study investigated two groups of women diagnosed with breast cancer in the south-east of Scotland between either 1957-1959 or 1997-1999 (ie 40years apart). The earlier group represent 1158 of 1207 women referred to radiation oncologists in the region and the later group comprised 1477 of about 1600 women referred to the Edinburgh Breast Unit. Whilst the age, menopausal status and laterality of the patients were similar in both groups, the tumour size and tumour location within the breast were significantly different in the two groups. Thus, there was significant reduction in T stage with year of diagnosis ($p<0.0001$), the incidence of T1, T2, and T3/4 being 15.6%, 51.9% and 25.6% in the earlier cohort compared with 49.3%, 36.8% and 13.7% in the later group. The overall distribution within the breast was significantly different by chi-squared analysis ($p<0.0001$). In terms of individual quadrants 469 of 1158 (40.5%) tumours were located in the upper outer quadrant (UOQ), whereas in the more recent cohort it was 788 of 1477 (53.4%), this increase in proportion being statistically significant ($p<0.0001$). Occurrence in the lower outer quadrant (LOQ) also significantly increased ($p<0.028$) but was significantly reduced in the upper inner quadrant (UIQ) and centrally (both $p<0.0001$). Analysing data on location for each T stage separately showed that the increased incidence in the UOQ with time was apparent for each subgroup. The increased incidence in UOQ tumours over time is therefore not a

simple reflection of decreased size between the two time groups. The underlying reason(s) for this change in distribution with time requires further study. Affluent women have a higher incidence of breast cancer than socially deprived women but may have a better outcome from the disease. The aims of the study in this thesis were to (i) quantify and investigate differences in survival and recurrence from breast cancer between women differing in socioeconomic status from the south-east of Scotland and (ii) define the contribution of underlying factors to this variation. To do this, 502 patients with non-metastatic invasive breast cancer referred to the Edinburgh Breast Unit between 1985 and 1993 were stratified according to Carstairs Index. This subdivides individuals into deprivation categories (DEPCAT) according to postal address. The most affluent have DEPCAT 1 and 2 and the most deprived areas are DEPCAT 6 and 7. The majority of women fell into DETCAT status 3 and 4 (25.1 and 27.1 respectively) whilst 10.4 and 16.3 % were placed in the most affluent DEPCAT 1 and 2 groups and 15.1, 2.6 and 3.4% in the most deprived DEPCAT 5, 6 and 7 groups respectively. To increase numbers in small groups and have approximately equal numbers, analyses were also performed combining DEPCAT scores1 and 2 to provide Zone A and DEPCAT scores 5,6 and 7 to provide Zone D (DEPCAT 3 was zone B and DEPCAT 4 was zone C). In terms of recurrence, there were trends for more affluent DEPCAT categories to have a better outcome but these did not reach statistical significance. However women from the most affluent zone had significantly better DFI than the socially deprived ($p= 0.0$ by Kaplan Meier).More affluent women (on the basis of either DEPCAT groups or zones) had a better survival compared to the most deprived. Based on single follow up time of 5 years, survival difference were statistically significant by chi-square analysis ($p=0.026$ for DEPCAT and 0.011 for zones). Furthermore, using the total follow-up until 2002, Kaplan Meier analysis of SES zones showed that affluent women had a significantly better survival ($p=0.02$). SES was not related to menopausal status or established prognostic factors such as lymph node status, tumour size and ER status, although lymph node status and tumour size were highly significantly associated with patient survival ($p<0.0001$ and 0.0006 respectively by Kaplan Meier). Given that these established factors do not relate to SES and that the patients were treated by defined

protocols irrespective of SES, the factors underlying the differences in outcome between affluent and deprived women in Edinburgh remain undefined. Further research is required to identify other reasons for poorer outcomes in deprived women, with a view to reducing these survival differences. These 2 studies provide further evidence for social factors influence the natural history of breast cancer.

CHAPTER 1

GENERAL INTRODUCTION

1.1 General Statistics Associated with Breast Cancer

1.1.1 Incidence

Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for a tenth of all new cancers and 23% of all female cancer cases [1]. Breast cancer is the commonest malignancy in females in Scotland; one woman in 15 can be expected to be affected with the disease by the age of 74. This is equivalent to a 6.6% lifetime risk of the disease [2]. During the 1980s, breast cancer accounted for 24% of all malignancy neoplasms in Scottish women, ie an average 2,660 new cases per year resulting in 1,250 breast cancer deaths per year.

There is a clear relationship between age and incidence. Overall the incidence of breast cancer rises with age. Thus, very few women under the age of 25 years develop breast cancer. Thereafter the incidence of the disease increases but plateaus at age 45-50 (which probably represents an effect of the menopause). Amongst young women in Scotland, in the decade to 1990, only 129 cases occurred under the age of 30 and 3,252 cases of breast cancer occurred in women under 45 years of age, this representing 8.1% of the total. Over half of the cases under 45 were in the age group 40-44 years [2]. The vast majority of breast cancers occur in older postmenopausal women.

Incidence increases more rapidly during the fourth decade of life and continues to increase thereafter, but more slowly in the fifth, sixth and seventh decades (after the menopause) [3]. In the USA, 75% of new diagnoses of breast cancer are in women aged 50 years or older. The cumulative incidence of breast cancer among women in Europe and North America is about 2.7% by age 55, about 5.0% by age 65, and about

7.7% by age 75 [4] and the lifetime risk of a diagnosis of breast cancer is approximately 12.5%.

The incidence of and mortality from breast cancer both vary about 5-fold between populations worldwide. Rates tend to be higher in more developed countries as compared with less developed countries, most notably in Africa and Asia [1].

The reason for this variation seems to be mainly environmental. In studies of migrants who move from low-risk to high-risk countries it is shown that rates increase and eventually become similar to those amongst the high-risk populations [5-7].

For example, breast cancer rates are about 4-7 times higher in the United States than in China or Japan. However, risk of breast cancer in Chinese, Japanese or Filipino migrants to the United States increases over several generations and approaches that among indigenous US Whites [6, 7].

Interestingly, the differences in the age-specific incidence of breast cancer are greatest after about age 50. For example, at the ages of 45 to 49, the incidence rates in the United States and Japan are 195 and 55 per 100,000 respectively but, after age 50, incidence in the United States continues to increase while in Japan it remains relatively constant. As a consequence, at 64 to 69 years, the rates for the United States and Japan are 404 and 53 per 100,000.

In Britain the age-standardised incidence of breast cancer per 100,000 women increased from 75 in 1979 to 116 in 2002. Over the twenty year period 1983-2002 the incidence rate increased by 45% [8-10]. The historically low rates in Eastern Europe and the Far East have begun to rise rapidly [11-13].

1.1.2 Mortality

Mortality from breast cancer among women varies significantly from country to country. The adjusted death rate per 100,000 women (1983-1987) was approximately 29 for England and Wales, 23 for US-white, 15 for Spain and 6 for Japan. Survival figures for England show that an average of 77% of women diagnosed with breast cancer in 1996 to 1999 were alive five years later [1, 14].

Although the breast cancer incidence rate has been increasing world-wide since 1950, mortality rates have levelled off or begun to decline recently. Most notably, the countries that have shown a downturn in mortality are generally those with the highest rates, whereas the countries with the lowest mortality rate tend to be the ones in which the mortality is increasing [15].

Increasing breast cancer survival, observed in most western countries, is not easily interpreted. It could be due to better treatment, more effective treatment due to earlier diagnosis or simply lead-time bias. Increased diagnostic activity (eg screening) can inflate both incidence and survival. The following patterns emerged (i) increasing survival with increasing incidence and declining or stable mortality (Sweden, Finland), (ii) slight survival increase, marked incidence increase and slight mortality decrease (Denmark, the Netherlands and France), (iii) increasing survival, marked decrease in mortality and tendency to incidence stabilization (UK), (iv) marked survival increase, steady or decreasing mortality and moderate increases in incidence (Spain, Italy), (v) stable survival, increasing incidence and mortality (Estonia). In most countries survival increased, indicating a real advantage for patients when accompanied by decreasing or stable mortality and attributable to improved cancer care (Sweden, UK, France, Italy and Spain). In Finland (with high survival), the Netherlands and Denmark increasing mortality and incidence indicate increasing breast cancer risk, probably related to lifestyle factors. In Estonia, low and stable survival in the context of increasing incidence and mortality suggests inadequate care [14].

1.2 Risk factors in breast cancer

In addition to age and country of residence as reviewed in 1.1.1, there are other factors which influence risk of breast cancer [5]. Many of these risk factors have a strong endocrine link such as menarche, menopause, childbearing, breastfeeding, obesity and anthropometric variables, levels of endogenous hormones and use of exogenous hormones (oral contraceptives and hormone replacement therapy).

1.2.1 Menarche

For each 1-year delay in menarche, the risk decreases by around 5% [16]. Although age at menarche is related to breast cancer risk at all ages, the effect may be stronger in younger (premenopausal) women. Relative risk for premenopausal breast cancer is reduced by an estimated 7% for each year that menarche is delayed after age 12 years, and by 3% for postmenopausal breast cancer [17-19]. Low risk countries such as China have a later average age at menarche (16-17 years).

1.2.2 Menopause

Menopause, either natural or induced, reduces risk of breast cancer and risk reduction is greater the earlier that menopause occurs. For example, incidence of breast cancer is about halved if the menopause occurs before age 45 years as compared to after age 55 years. Risk increases by about 3% for each year older at menopause [4].

The menopause is probably responsible for the slowing in the rate of increase in breast cancer incidence with age that occurs at around age 50. Thus, premenopausal women are at higher risk of breast cancer than postmenopausal women of the same age, and perimenopausal women are at intermediate risk [4, 17].

The effects that early menarche and late menopause have in increasing risk suggest that the number of menstrual cycles that a woman has may be an important determinant of risk, and that risk may be reduced in those with prolonged amenorrhea [16, 17].

1.2.3 Childbearing

That parity reduces the risk of breast cancer has long been recognized. In the 18th century Bernado Ramazzini reported the high rate of breast cancer in nuns compared with married women and speculated that this might be associated with their lack of children. Subsequently, it was shown that women who had at least one full-term pregnancy compared with nulliparous women on average have around a 25% reduction in breast cancer risk [20]. In a meta-analysis nulliparity was associated with a 30% increase in risk compared with parous women [21].

Some evidence suggests that the earlier the full-term pregnancy, the earlier the period of decreased susceptibility of breast tissue changes begins [17]. The relative risk of developing breast cancer increases by 3% for each year of delay [22]. The age at first full-term pregnancy affects risk of breast cancer independently of the total number of pregnancies; protection is greater the younger the age at first birth [17]. In a meta-analysis of studies from Nordic countries, women who had their first birth when younger than 20 years had a 30% lower risk of breast cancer than those with a first birth after the age of 35 [21].

Furthermore, increasing protection is seen with increasing numbers of full-term pregnancies, such that women with five or more children have about half the risk of nulliparous women [21]. In the absence of breast feeding there is a reduction in risk of 7% for each birth after the first [22].

However, the effect of childbearing is complex. Thus it may have a dual effect on risk of breast cancer; incidence is increased in the period immediately after a birth,

but this excess risk gradually diminishes and, as discussed above, in the longer term the effect of a birth is to protect against the disease [20]. To complicate matters, a first pregnancy very late in reproductive life (after age 35 years) may increase risk beyond that in nulliparous women.

1.2.4 Breastfeeding

The effect of breastfeeding on risk of breast cancer is controversial, probably because the effect is small. However studies in less developed countries, where the total duration of breastfeeding can be very long, have reported substantial protective effects [23].

Protection has also been seen in some, but not all, studies in more developed countries. For example, the US Cancer and Steroid Hormone Study examined the relation between breastfeeding and breast cancer in over 4,500 women with the disease and found that women who had breastfed for a total of 25 months or more had a 33% lower risk of breast cancer than those who had never breastfed, with adjustment for parity and age at first full-term pregnancy [20]. The relative risk of breast cancer decreased by 4.3% (95% CI 2.9-5.8; $p<0.0001$) for every 12 months of breastfeeding in addition to a decrease of 7.0% (5.0-9.0; $p<0.0001$) for each birth. The size of the decline in the relative risk of breast cancer associated with breastfeeding did not differ significantly for women in developed and developing countries, and did not vary significantly by age, menopausal status, ethnic origin, the number of births a woman had, her age when her first child was born or any of nine other personal characteristics examined. The lack of or short lifetime duration of breastfeeding typical of women in developed countries makes a major contribution to the high incidence of breast cancer in these countries [22].

1.2.5 Obesity and anthropometric variables

In postmenopausal women, obesity increases the risk of breast cancer; risk is about 50% higher in obese women (body-mass index >30 kg/m^2) than in lean women (body mass index 20 kg/m^2). This association is not observed in premenopausal women among whom some, but not all, studies have observed that risk is slightly lower in obese women than in women of normal weight [24-26].

Adult height shows a weak positive association with breast cancer risk [27, 28]. Average height is substantially greater in populations with high rates of breast cancer than in populations with low rates. Within populations, a 10 cm greater height is typically associated with an increase in risk of about 10% [29] and there was an approximate increase in relative risk of 7% for each additional 5 cm in height for postmenopausal women and 2% for premenopausal women [28].

The underlying mechanism for the association between height and breast cancer risk is unclear, and it is likely that height may be a marker for other exposures that influence breast cancer risk [27].

1.2.6 Endogenous Hormones

There are only a few prospective studies on endogenous sex hormone levels and breast cancer risk [30]. The risk for breast cancer increased statistically significantly with increasing concentrations of all sex hormones examined: total oestradiol, free oestradiol, non-sex hormone-binding globulin (SHBG)-bound oestradiol (which comprises free and albumin-bound oestradiol), oestrone, oestrone sulfate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate and testosterone.

Amongst the sex hormones, oestrogens have been most consistently linked with risk of breast cancer. Associations have been proposed with total lifetime exposure to

oestradiol, exposure to bioavailable oestradiol, exposure to oestrogen plus progesterone, or exposure to oestradiol at times of progesterone insufficiency that may exist during menarche and the perimenopausal period [31]. Low serum oestradiol concentrations have been found in premenopausal populations at low risk of breast cancer [32]. In postmenopausal women, several prospective nested case-control studies have linked raised oestrogen concentrations after the menopause with subsequent breast cancer development [4, 33, 34]. Studies of postmenopausal women in populations with different risks of breast cancer have generally shown that women from the population with the higher risk country have an overall mean level of serum oestradiol about 20 per cent higher than women from low risk countries. These comparisons have included American whites and Asian migrants to Hawaii, women in Britain and China, and women in the United States and Japan. The factors responsible for these differences in oestradiol levels are not yet known, but they may be due to differences in body fat and in diet. The effect of obesity in increasing risk in postmenopausal women may be due to increased blood levels of oestradiol produced from androstenedione in adipocytes.

1.2.7 Exogenous sex hormones

Oral contraceptives

Oral contraceptives were introduced in the early 1960s, and only relatively young women have had the opportunity to use them from the start of their reproductive lives. Substantial numbers of women with prolonged exposure to oral contraceptives early in life have only recently entered the age group where breast cancer is common, and the full impact of long-term oral contraceptive use on breast cancer risk may not yet have been seen. It is also possible that breast tissue still undergoing development in the young may be more susceptible to the effects of hormones and at greater risk of developing cancer after exposure. The literature suggests that early exposure to oral contraceptives, either by use in adolescence, or use before age 25 years, or prolonged use before first pregnancy, may increase risk.

However, contradictory evidence exists in each of these areas. The risk of breast cancer is increased by around 25% in current users of combined oral contraceptives, but the excess risk falls after cessation of use, such that 10 or more years after use stops, no significant increase in risk is evident. The effect on risk of breast cancer does not vary with the type of oestrogen or progestogen used. Although data on progestogen-only oral contraceptives are limited, their effects seem to be broadly similar to those of combined preparations [34].

Use of combined oral contraceptives is associated with a larger excess of localised cancers than those that have spread beyond the breast [34]. This finding has raised the possibility that the increased risk of breast cancer in recent users of oral contraceptives may be partly due to increased surveillance.

Hormone replacement therapy

Increasing numbers of women in their 50s and 60s are using hormone replacement therapy to alleviate menopausal symptoms. The effect of long term use of these agents in women aged over 50 on the breast is only now becoming apparent.

Worldwide data on the relationship of hormone replacement therapy (HRT) to breast cancer risk have been analysed by the Collaborative Group on Hormonal Factors in Breast Cancer [34]. HRT increases risk of breast cancer in current and recent users (within five years). Risk increases by about 2% for every year of use. The magnitude of the effect of HRT on risk of breast cancer is similar in magnitude to that of a delayed menopause. Between age 50 and 70 cumulative incidence is 45 per 1,000 in non-users, and is increased by 2 in users for 5 years, and by 6 in users for 10 years. The effect of HRT on risk appears to be greater among women of lower body weight. There appears to be no increased risk of breast cancer among women who stopped using HRT more than 5 years previously, regardless of the length of time that they had taken HRT [34]. The risk of having breast cancer diagnosed is increased in women using HRT and increases with increasing duration of use. This effect is

reduced after cessation of use of HRT and has largely, if not wholly, disappeared after about 5 years [35].

Studies have reported significantly higher levels of risk of breast cancer in women taking combined oestrogen and progestogen preparations compared with women taking oestrogen alone [36].

Xenoestrogens

Some compounds that are environmental contaminants have weak oestrogenic properties. These compounds include polychlorinated biphenols (PCBS), and the pesticide DDT and its metabolites. These and other similar compounds are persistent environmental pollutants that have been found in fish, wildlife and humans. Most epidemiological studies have not found evidence to support the hypothesis that exposure to PCBS and DDT increases risk of breast cancer [37].

1.2.8 Family history

The evidence for genetic predisposition to breast cancer derives originally from observations of cancer clustering in families and cancer risk increasing in individuals with some genetically determined syndromes. Individuals with a family history of breast cancer are at increased risk of developing the disease. The magnitude of the increase in risk in an individual is influenced by the number of relatives affected, by the age at onset in those affected and by their relationship to the individual. The risk of the cancer is approximately doubled in first-degree relatives (mothers, sisters, daughters) of affected patients [38, 39]. With affected second-degree relatives (grandmothers, aunts, grand-daughters), there is a lesser increase in risk. Risk to relatives is greater when there is early onset or bilateral disease in those affected. At least some of the increased risk associated with a family history of breast cancer is due to the inheritance of genes that predispose to the disease. Environmental and lifestyle factors rather than inherited genetic factors account for most cases of breast

cancer. Less than 10% of women in the general population have a family history of breast cancer [40]. Most women with the disease do not have a family history of it, and most women with affected relatives never develop breast cancer.

About 5-10% of cases of breast cancer are due to germline mutations in cancer - susceptibility genes showing autosomal dominant inheritance. Two genes, *BRCA1* and *BRCA2*, have been isolated and shown to be the cause of up to 80% of large breast cancer kindreds [41].

Despite the obvious importance of mutations in *BRCA1* and *2* in the aetiology of breast cancer, mutations in these genes are present in only a small proportion of subjects with breast cancer.

1.2.9 Dietary variables

International differences in the incidence of breast cancer, and the results of animal experiments, suggest that diet may play an important role in the aetiology of breast cancer [42]. Although there are several components of the diet for which there is some evidence of an influence on the risk of breast cancer, the strength of the evidence varies and in some areas it is the subject of considerable controversy. The available evidence suggests that increased intake of energy, of dietary fat, meat and alcohol may all increase risk [43, 44] and that increased intake of fibre, fruits and vegetables, antioxidant vitamins and phytoestrogens may all reduce risk [5].

1.2.10 Physical activity

A recent report from the International Agency for Research on Cancer concluded that physical activity has a preventive effect on breast cancer [25]. This may be an indirect effect with exercise lowering BMI, or a direct effect on hormonal and growth factor levels. The magnitude of this effect varies between studies; a typical result is a

30-40% reduction in the risk of breast cancer with a few hours per week of vigorous activity versus none [45].

Physical activity is associated with leanness, later onset of menarche and with a greater frequency of amenorrhea, all factors associated with a reduced risk of breast cancer. Two of four cohort studies and two case-control studies have shown that physical activity is associated with a reduced risk of breast cancer [25, 45].

Several studies have reported that moderate physical activity is associated with a lower risk of breast cancer. The data are not entirely consistent, although they are somewhat stronger for premenopausal women than for postmenopausal women [45].

1.2.11 Exposure to Radiation

Epidemiological studies in humans show that exposure to radiation increases risk of breast cancer. The evidence comes from the follow-up of individuals exposed to radiation in a variety of circumstances including atomic bomb explosions in Japan, fluoroscopic chest radiography for tuberculosis, and therapeutic radiation for benign and malignant conditions. Studies in these different populations of subjects suggest that risk of breast cancer increases between 5 and 10 cases per 10,000 for every G ray of exposure. The effect of exposure to radiation on risk of breast cancer is strongly influenced by age at the time of exposure. Risk is greatest among women aged less than 20 at exposure, and least among those aged more than 40 years. Exposure in early childhood may also increase risk.

A recent study estimated that exposure to diagnostic x-rays may be responsible for 29 cases per year of female breast cancer before the age of 75 in the UK, an attributable risk of 0.1% [46]. Overall, 0.6% of the cumulative risk of cancer to age 75 might be radiation-induced in the UK - approximately 700 cases of cancer each year.

1.2.12 Previous Benign Disease

The majority of women who undergo breast biopsy are not at increased risk of breast cancer. The histologically heterogeneous group of 'benign breast diseases' is often divided into non-proliferative lesions and proliferative lesions without or with atypia. Non-proliferative lesions are generally associated with little or no increase in risk of breast cancer [47]. Proliferative lesions without atypia confer an increase in risk of about twofold and atypical hyperplasias an increase of at least four-fold compared with women without benign breast disease.

1.2.13 Radiographical breast density

The radiographic appearance, or mammographic pattern, of the female breast varies between individuals because of differences in the relative amounts of fat, connective and epithelial tissue [48]. Mammographic pattern is associated with age and menopausal status; the breasts of young, premenopausal women are generally of greater radiodensity than those of older, postmenopausal women [49].

At least 13 cohort studies, or case-control studies nested in cohorts, have demonstrated that radiologically dense breasts have an increased risk of breast cancer. The risk of breast cancer in women with extensive breast tissue visible on a mammogram have a risk of breast cancer that is 1.8 to 6.0 times that of women of the same age with little or no density [50]. The decline in breast density with age, and the significant increase after initiation of oestrogen-replacement therapy, suggest that the tissue changes are reversible and under hormonal control [51].

1.3 Natural History of Breast Cancer

Breast cancer usually starts by an abnormal and uncontrolled growth of cells lining the lobule terminal duct unit [52].

The most common type of non-invasive breast cancer is ductal carcinoma in situ (DCIS). If not treated this may develop into an invasive form of breast cancer. The most common type of invasive breast cancer is called invasive ductal carcinoma (IDC). Around three in four people with breast cancer have this type [53].

The staging of breast cancer involves clinical, pathological and radiological data, a commonly used classification system is the TNM (Tumour, Nodes, Metastases) system which stage a tumour according to the size and extent of local spread of the tumour, the presence of lymph node metastases, and the presence of distance metastases (usually to the liver, bone, lung and brain).

In the UK the majority of breast cancer cases are early breast cancers, diagnosed usually at TNM staging T1 and T2 [54].

Surgical concept assumes that cancers grow and spread in an orderly manner, from primary cancer to regional lymph nodes and finally to vital organs. When breast cancer spreads beyond the breast, it is said to be "metastatic", meaning that it has travelled from the breast to another part of the body. Cancer cells can travel through either the lymphatic system or the blood vessels.

There are two types of metastatic breast cancer. When the cancer cells travel from the breast to the under arm (axillary) lymph nodes, it is still considered an "early" or potentially curable breast cancer. With proper surgery and systemic treatments, there is still a good chance that all cancer can be removed from the body.

If the cancer has travelled past the lymph nodes to another part of the body, a woman is said to have "distant metastasis". The most common places that breast

cancer spreads to are the bones, the liver and the lungs. Many treatments are available for breast cancer that has spread to other parts of the body, but unfortunately once cancer has escaped from the breast and underarm lymph nodes, it is no longer curable [53, 55].

1.4 Treatment

Treatment of breast cancer depends upon a variety of factors such as menopausal status of the patient, type of breast cancer, tumour size, histological grade and stage (early breast cancer locally advanced or distant metastatic) and co-morbidity. The main treatment modalities for breast cancer are surgery, radiotherapy, hormone therapy, chemotherapy and biological response modifiers.

1.4.1 Early breast cancer

Because the disease is apparently restricted to the breast, the primary treatment for early breast cancer (EBC) is breast surgery plus local radiotherapy. In high-risk women consideration needs to be given to some form of adjuvant systemic therapy for occult micrometastases.

Breast-conserving surgery and radiation

Clinical trials have demonstrated that women with early-stage breast cancer who receive breast-conserving surgery followed by radiation have survival outcomes similar to those of women who receive a mastectomy [56]. A 1990 NIH Consensus Development Panel concluded that "breast conservation treatment (breast-conserving surgery followed by radiation therapy) is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast" [56]. Breast-conserving surgery followed by radiation therapy is associated with a lower rate of local recurrence than breast-conserving surgery alone [56, 57].

Adjuvant systemic therapy in high risk, lymph node positive patients

Chemotherapy may be given to high risk patients (based on patient's age, the size of the tumour, grade of the tumour and presence or absence of lymph node involvement). When used as adjuvant therapy after breast conservation therapy or mastectomy, chemotherapy reduces the risk of breast cancer recurrence, either as an adjuvant or neoadjuvant therapy. Meta-analyses have shown that the benefits of chemotherapy are greater in premenopausal women as compared with their postmenopausal counterparts. Clinical research studies over the last 30 years have determined which combinations of chemotherapy drugs are most effective. However, the "best" combination may not have yet been discovered, so there continue to be clinical research studies comparing one of today's most effective treatments against something that may be better. However, the most commonly used combinations are:

- Cyclophosphamide (Cytoxan), methotrexate (Amethopterin, Mexate, Folex), and fluorouracil (Fluorouracil, 5-FU, Adrucil) [abbreviated CMF]
- Cyclophosphamide, doxorubicin (Adriamycin), and fluorouracil [abbreviated CAF]
- Doxorubicin (Adriamycin) and cyclophosphamide [abbreviated AC]
- Doxorubicin (Adriamycin) and cyclophosphamide followed by paclitaxel (Taxol) or docetaxel (Taxotere) [abbreviated AC -->T] or docetaxel concurrent with AC [abbreviated TAC]
- Doxorubicin (Adriamycin), followed by CMF
- Cyclophosphamide, epirubicin (Ellence), and fluorouracil [abbreviated CEF] with or without docetaxel
- Cyclophosphamide and Docetaxel (TC)
- Gemcitabine (Gemzar) and paclitaxel (Taxol) [abbreviated GT]

Adjuvant hormonal therapy

In patients with oestrogen receptor-positive tumours, hormone therapy has been shown to produce significant clinical benefits including overall survival [35]. In premenopausal women consideration can be given to oophorectomy and LHRH agonists, whereas in postmenopausal women until recently tamoxifen was recommended [58] although aromatase inhibitors are increasingly used (see section below).

1.4.2 Advanced breast cancer

When the tumour has progressed beyond the breast, it is essential to treat disseminated disease. Locally advanced disease may be treated with radiotherapy and/or neoadjuvant systemic therapy followed by local surgery [59]; but distant metastatic disease invariably requires systemic therapy (either chemotherapy or endocrine therapy).

Endocrine therapy

Oestrogen sensitive cancers make up around 75% of breast cancers in postmenopausal women and around 50-60% in premenopausal women. Measurement of oestrogen receptors is the single best parameter by which to identify hormone sensitive tumours.

Current guidelines recommend that patients with ER-positive tumours should have hormone therapy, whereas those with ER-negative tumours should have chemotherapy. Whilst tamoxifen until recently has been the first choice drug, the efficacy of third-generation aromatase inhibitors has been clearly proven in trials in metastatic breast cancer [60]. In premenopausal women LHRH agonists either alone or in combination with other drugs has been shown to be effective in metastatic disease [59].

Chemotherapy

Systemic chemotherapy for breast cancer may produce clinical benefits in advanced breast cancer. Overall response rates to chemotherapy are about 40-60% with a median time to relapse of 6-10 months. Analogues of the most potent drug (Doxorubicin) are most commonly used. The main reason for considering them is a greater safety margin [61].

Some other chemotherapy drugs used for treating women with breast cancer include carboplatin (Paraplatin), cisplatin (Platinol), vinorelbine (Navelbine), capecitabine (Xeloda), pegylated liposomal doxorubicin (Doxil), and albumin-bound paclitaxel (Abraxane).

Biological therapy

One such drug, trastuzumab (Herceptin), targets breast cancer cells that have a protein called HER2 on their surface [62]. Trastuzumab is currently licensed for the treatment of women with advanced breast cancer who have a particular genetic flaw that produces the protein HER2. It is also being used in some women with early-stage breast cancer as part of clinical trials and has shown promising results [63].

1.5 Prognosis

Prognosis of breast cancer is variable and even women with the same stage of disease despite treatment/no treatment may have different outcomes, hence the need for prognostic factors to spare those who have indolent disease the side-effects of treatment but to ensure those with aggressive disease are not undertreated. Prognosis prediction for patients with breast cancer is currently based on histopathological typing and oestrogen receptor positivity, although patients with same staging may have disparate outcomes, which may indicate that the prognosis is multifactorial and no individual factor is definitive. Prognostic factors can be broadly classified into two groups: chronological factors, which are indicators of how long the cancer has been present and relate to stage of disease at presentation, and biological factors, which relate to the intrinsic or potential behavior of the tumour [64, 65].

1.5.1 Chronological factors

Tumour size

The pathological size of a tumour correlates directly with survival - patients with smaller tumours have a better survival rate than those with large tumours [64-68].

Status of axillary lymph nodes

Axillary lymph node status has repeatedly been shown to be the single most important predictor of disease-free survival and overall survival in breast cancer. Survival of patients with breast cancer according to involvement of axillary lymph nodes is 64.9% for negative axillary lymph nodes and 45.9% for positive axillary lymph nodes, at 10 years for all patients.

Only 20-30% of node-negative patients will develop recurrence within 10 years, compared with about 70% of patients with axillary nodal involvement. The absolute number of involved nodes is also of prognostic importance. Patients with 4 or more involved nodes have a worse prognosis than those with fewer than 4 involved nodes [69, 70].

Metastases

Patients in whom cancer has spread beyond the axillary or internal mammary nodes (M1 or stage IV disease) have a much worse survival rate than patients whose disease is apparently localized. For example, patients with Stage IV disease only have an 18% chance of surviving to 5 years compared with 84% with Stage I, 71% with Stage II (Stage III has an intermediary survival of 48%) [71]. There are differences in survival between patients depending on the site of the metastatic disease, with patients who have supraclavicular involvement as their only site of metastases having a much better survival rate than patients with metastases at other sites.

Age at diagnosis

Recent evidence suggests that age at diagnosis may also be a risk factor: younger women (aged under 35) have a poorer prognosis than older patients with cancer of equivalent stage [70].

1.5.2 Biological factors

Histological type

Many of the so called special types of invasive breast carcinoma (invasive tubular, cribriform, mucinous, papillary and microinvasive) are associated with a much better prognosis than cancers of no special type. Histological type is one of the best predictors of long term survival [72].

Histological grade

The three characteristics of tubular formation, nuclear pleomorphism and mitotic frequency are assessed in a semiquantitative manner to give three histological grades (I, II, and III) which correlate directly with survival. Survival of patients according to histological grade of tumour is 85% for grade I, 60% for grade II and 40% for grade III [73]. Histologic grade is an important determinant of prognosis that also allows risk stratification within a given tumour stage [74-77].

Lymphatic or vascular invasion

Tumour cells can be identified in lymphatic and blood vessels in up to a quarter of all patients with breast cancer. Their presence is associated with at least a doubling of the rate of local recurrence after wide local excision or mastectomy and patients with this feature are at high risk of short term systemic relapse.

Peritumoural vascular invasion (either blood vessel or lymphatic channel) is predictive of local failure and reduced overall survival [78]. Although some studies have found no correlation with clinical outcome, this may be a reflection of differences in distinguishing true vascular space invasion from retraction artifact.

Markers of proliferation

Patients with tumours that have a high rate of proliferation have an increased rate of local recurrence and a worse survival rate than patients whose tumours proliferate slowly. Several methods to measure proliferation have been reported, including measurement of the fraction of cells in the S phase of the cell cycle, the use of monoclonal antibodies such as Ki67, KiS1, and MIB-1, and identification of proliferating cells by the use of tracers such as bromodeoxyuridine. These measurements may be used to stratify patients into good and poor prognostic groups [79-83]. The monoclonal antibody MIB-1 recognizes Ki-67 but can be used in formalin-fixed, paraffin-embedded tissue sections. Several studies have suggested that MIB-1 may have greater predictive value than anti–Ki-67 [82].

Hormone and growth factor receptors

The presence of oestrogen receptors in a breast cancer predicts response to hormonal manipulation. This appears to be of some value in predicting early outcome after treatment but is of limited value in predicting long term survival. Progesterone receptors can be identified in some breast cancers. Their presence depends on an intact oestrogen receptor pathway, but it is not clear that they are of more value than oestrogen receptors in predicting prognosis or response to hormonal treatment. One study showed women with oestrogen receptors in their tumours survived significantly longer than those without receptors; this was true for both premenopausal and postmenopausal women and also when the patients were subdivided into those with and without axillary metastases. Patients with axillary metastases and no oestrogen receptors in their tumours had the worst prognosis, while women with axillary metastases and oestrogen receptors had a death rate similar to that of women with no axillary metastases and no receptors. The oestrogen-receptor (ER) content of the primary tumour was measured in 133 postmenopausal women with operable breast cancer. Fifty nine (59%) were positive

for oestrogen and 54 (41%) negative. Curves of life survival show that women with ER-positive tumours live longer than those with ER-negative tumours [84-86].

The presence of epidermal growth factor receptors within the membrane of breast cancer cells is inversely correlated with the presence of oestrogen receptors [87-90] and is associated with a diminished period free of relapse and reduced overall survival [91].

However, studies of the prognostic significance of EGFR expression have provided mixed results, with only some studies showing a correlation between EGFR and poorer disease-free survival [89, 90, 92, 93].

c-erbB2 (Her2-*neu*)

c-erbB2 altered breast cancer is associated with high histologic grade and reduced survival [94-97]. c-erbB2 is overexpressed in 15-30% of invasive cancers [98, 99] and in up to 80% of non-invasive cancers, and its product is homologous with the epidermal growth factor receptor. Patients with lymph node involvement whose tumours express c-erbB2 have a particularly poor prognosis, but c-erbB2 seems to be of less value in delineating the prognosis of patients who are lymph node negative. Tumours which express c-erbB2 are more likely to be resistant to both chemotherapy and hormonal treatment. Thus, c-erbB2 analyses are requested to obtain prognostic (outcome independent of treatment) and predictive (outcome dependent on treatment) data [100].

p53

The product of the gene seems to be a transcription factor responsible for checking the fidelity of cell replication. Nearly one third of breast cancers have mutations of the tumour suppressor gene p53, which are associated with high histologic grade and clinical aggressiveness [101-105].

Immunohistochemical assays generally detect overexpression of the gene, which is often related to conformational alterations and a prolonged half-life of the encoded protein [106, 107]. Given the diverse functions of the p53 gene and the location and type of genetic abnormalities (including gene loss and point mutation), the specific genetic lesion may be shown to have prognostic importance.

p53 appears to be a useful prognostic marker, particularly in node-negative breast cancer patients [108], and may also help identify patients likely to respond to chemotherapy or radiotherapy. Patients with p53-immunopositive cancers may develop autoantibodies against p53, which have been used by some to detect or follow cancers [109].

Proteases

Cathepsin D is a lysosomal proteinase that is overexpressed in some breast cancers. Overexpression of cathepsin D is associated with several poor prognostic features, such as high histologic grade, large tumour size and node positivity, and has been reported to be associated with an increased risk of recurrence and reduced disease-free survival. However, while some studies have suggested that cathepsin D is an independent prognostic factor in node-negative patients, others show no prognostic significance among node-negative patients [110-112].

Interrelated factors

Many of the factors which correlate with outcome are interrelated and do not therefore have independent prognostic significance. For example, grade III tumours are likely to be oestrogen receptor negative, to be epidermal growth factor receptor positive, have a high proliferative index and to be aneuploid. When a multivariate analysis is performed and histological grade is entered first, little further prognostic information is obtained by entering these other factors. Measurements of large

numbers of prognostic factors is therefore of no value in the routine management of patients with breast cancer.

Prognostic indices

Although individual factors are useful, combining independent prognostic variables in the form of an index allows identification of groups of patients with different prognoses. The Nottingham prognostic index is the most widely used index and incorporates three prognostic factors: tumour size, node status and histological grade [113]. With the Nottingham index the lymph node stage is 1 if no nodes are involved, 2 if one to three nodes are involved, and 3 if four or more nodes are involved. The Yorkshire Breast Cancer Group categorised lymph node stage as 1 if no nodes were involved or 3 for any axillary node involvement. The Yorkshire group also used different codes for tumour grade: code 1 for grade I and code 2 for grades II and III. Both indices identify three prognostic groups. The good prognostic group has a survival similar to that of age matched controls without breast cancer, and such women are unlikely to benefit from aggressive forms of adjuvant treatment. In contrast the poor prognostic group, with a 13% survival after 15 years, may well benefit from more intensive systemic treatment. (Nottingham prognostic index = (0.2 x size) + lymph node stage + grade.)

Prognostic factors are of value for three main reasons:

- To help select the appropriate treatment for individual patients
- To allow comparisons of treatments between groups of patients at similar risks of recurrence or death
- To improve our understanding of breast cancer, which may permit the development of new strategies or treatments

1.6 Race/Ethnicity

Race has been shown to influence breast cancer prognosis, although this may be related to socioeconomic status [114-118].

In one study, a 5-year relative survival from breast cancer for White and African American females by stage for cases diagnosed during the intervals 1975-1979 and 1995-2001, found relative survival is consistently lower in African American than in White women (although it has improved over time in both, except for distant stage disease among African American women). For White women, 5-year relative survival increased from 90.7% to 98.5% for localized disease, 68.8% to 82.9% for regional stage disease, and from 18.0% to 27.7% for distant stage disease. Among African Americans, relative survival increased from 84.8% to 92.2% for localized disease, and 55.1% to 68.3% for regional stage disease, but there was minimal improvement (15.1% to 16.3%) for distant stage disease [119].

Mortality rates vary by race and ethnicity. In the period 1998-2002, the average annual female breast cancer death rate was highest in African Americans (34.7 cases per 100,000 females), followed by Whites (25.9), Hispanics/Latinas (16.7), American Indians/Alaska Natives (13.8), and Asian Americans/Pacific Islanders (12.7).

The higher death rate among African Americans, despite the lower incidence rate, is due to both later stage at diagnosis and poorer stage-specific survival [119].

1.7 Socioeconomic Status

SES is also a factor which influences prognosis and outcome. Breast cancer patients from socially deprived areas have poor survival as compared with those who are more affluent [120-122]. This is reviewed in more detail in the introduction to Chapter 3. Social and economic factors within racial/ethnic groups are being examined as risk factors not only for breast carcinoma mortality and survival but also as determinants of the rate of incidence. Social and economic factors have been associated in the literature predominantly with cancer mortality and survival. When socioeconomic status (SES) is considered, certain studies suggest that racial disparities in breast carcinoma are smaller than when social and economic factors are examined alone, but these disparities still persist [123].

CHAPTER 2

CHANGES IN THE SITE OF CANCER WITHIN THE BREAST WITH TIME

2.1 Introduction

Numerous clinical studies, dating back decades, have shown that the upper outer quadrant (UOQ) of the breast is the most frequent site of carcinoma, but an adequate explanation for this asymmetric occurrence of breast cancer within the breast has never been established. This basic observation has become textbook fact [124] and remains true for countries as different as India [125], the West Indies [126] and Italy [127] and irrespective of race within any one country [128].

Furthermore, the UOQ is not only the most common site for cancer but also, in many benign breast conditions, fibroadenomas, breast cysts [129] and phyllodes tumours [130]. The UOQ is also the most frequent site of male breast cancer [131, 132].

However, it is interesting to note that the reported incidence of breast cancer in the UOQ of the breast appears to rise disproportionately with year of publication. In 1926, 30.9% of breast cancer was reported to be in the UOQ [133] but reports between the years 1947-1967 suggested that the proportion of breast cancer in the UOQ was 43-48% [134, 135, 136, 137]. A study in 1994, reported 60.7% of breast cancers in the UOQ [127]. Most of these studies are old.

In a recent study in the UK, female breast cancer incidence was studied in England, Wales and Scotland. Over the period 1979 to 2000, the incidence of female breast cancer has increased in England and Wales from 74.4 per 100,000 population (European age-standardised rate (EASR)) (21,446 new cases recorded) in the year of 1979 to 113.8 per 100,000 population (EASR) (35,903 new cases recorded) in the year

of 2000. Within the 212,677 cases made with site-specific information between 1979 and 2000, 52.5% of the cases were in the UOQ of the breast (111,583 cases recorded). Other sites in the breast were found at lower frequencies: 3.9% in the nipple and areola (8,222 cases recorded), 11.2% in the central portion (23,780 cases recorded), 14.6% in the upper inner quadrant (31,064 cases recorded), 6.4% in the lower inner quadrant (13,570 cases recorded), 9.8% in the lower outer quadrant (20,836 cases recorded) and 1.7% in the axillary tail (3,622 cases recorded). Inspection of the annual incidence rates for each of these sites in the breast shows that as the incidence of breast cancer has risen overall between 1979 and 2000, it is also increasing in all of these sites. However, it does not appear to be increasing in all quadrants relative to one another at the same rate. In Scotland, the incidence of female breast cancer has risen from 84.9 per 100,000 population (EASR) (2,480 new cases recorded) in the year of 1980, to 109.8 per 100,000 population (EASR) (3,485 new cases recorded) in 2001. Within the 17,911 returns made with site-specific information between 1980 and 2001, the site of greatest incidence within the breast was again the UOQ in 52.6% of the returns (9,418 cases recorded).

As for the data for England and Wales, no other quadrant showed any significant increase over the total. Over a 21 year time span, incidence of breast cancer in the UOQ has risen disproportionately from 38.3% in 1980 to 54.7% in 2001 [138]. However the factors involved remain contentious, but it has been suggested that tissue mass is an important contributor to asymmetry in cancer incidence [139]. This has been attributed to more epithelial cells on the left side of the body due to preferential vascular supply to the left side of the body during intrauterine cardiac development [140].

Several investigations in patients with breast cancer have presented data which show that the prevalent site of the primary tumour is the upper outer quadrant [124, 134, 135, 140-142].

In a recent study done in Nottingham the quadrant from which 746 consecutive breast core biopsies reported as normal, benign or malignant was recorded. The distribution in the breast of normal, benign and malignant results were comparable. In particular, the proportion of core biopsies from the upper outer quadrant reported as normal (67%, 95% confidence interval 59-74%), benign (57%, 95% confidence interval 51-63%) or malignant (62%, 95% confidence interval 57-67%) were similar. This result supports the hypothesis that the high proportion of upper outer quadrant carcinomas of the breasts is a reflection of the greater amount of breast tissue in this quadrant [143]. However, other workers have also queried explanatory dogma through their studies showing an even distribution of cancer between quadrants in large and small breasts, despite the less marked quadrant distribution of tissue in the smaller breasts [129].

An alternative explanation of this could simply be that the upper outer quadrant is the local area in vicinity to the axilla where deodorants and antiperspirants are applied. Since they are applied in large amounts, they may simply penetrate through the skin of the local area and mimic the effect of oestrogen in the breast tissue [138].

The importance of tumour location has an important role in the prognosis of breast cancer as it has been proved that early breast cancers situated in central/ internal quadrants have a worse prognosis compared with those in lateral quadrants, in terms of distant metastases and survival. Data from 2,396 patients treated for early breast cancer with a conservative approach were reviewed (1973 to 1989). In 1,619 patients the tumour had a lateral site, while in 777 cases it was situated in the internal/central quadrants. The characteristics of the two groups were well balanced, apart from axillary nodal metastases, which were more frequent for lateral tumours (38.1% v 26.3%). The result of this analysis of distant metastases indicated that the regression coefficient associated with tumour site was significant and the hazards ratio estimate was 1.291, which indicates the risk of distant metastases was increased by approximately 30% for internal/central tumours [144].

In another study [145], medial location was associated with a 50% excess risk of systemic relapse and breast cancer death compared with lateral location. Five-year systemic disease-free survival rates were 66.3% and 74.2% for high-risk medial and lateral lesions respectively ($p < 0.005$). Corresponding 5-year disease-specific survival rates were 75.7% and 80.8% respectively ($p < 0.03$).

A similar study in Switzerland [146] showed 10 year disease-specific survival was 93% (95%CI: 91–94%). Patients with breast cancer of the lower-inner quadrant (n = 118; 7.8%) had an increased risk of dying of breast cancer compared to women with breast cancer of the upper-outer quadrant (multi-adjusted Hazard Ratio: 2.3, 95%CI: 1.1–4.5, $p = 0.0206$). The over-mortality associated with this quadrant was particularly evident for tumours >10 mm (multi-adjusted HR: 3.6, 95%CI: 1.6–7.9, $p = 0.0016$). There was no increased breast cancer mortality risk for tumours located in other quadrants.

Another study from Italy [147], showed statistically significant differences for patients with medial tumours versus those with non-medial tumours in disease-free survival (DFS; 10-year DFS, 46% *v* 48%; HR, 1.10; 95% CI, 1.02 to 1.18; $p = 0.01$) and overall survival (10-year OS 59% *v* 61%; HR, 1.09; 1.01 to 1.19; $p = 0.04$). This difference increased after adjustment for other prognostic factors (HR, 1.22; 95% CI, 1.13 to 1.32 for DFS; and HR, 1.24; 95% CI, 1.14 to 1.35 for OS; both $p = 0.0001$). The risk of relapse for patients with medial presentation was largest for the node-negative cohort and for patients with tumours >2 cm. In the subgroup of 2,931 patients with negative axillary lymph nodes, 10-year DFS was 61% *v* 67%, and OS was 73% *v* 80% for medial versus non-medial sites, respectively (HR 1.33; 95% CI, 1.15 to 1.54; $p = 0.0001$ for DFS; and HR 1.40; 95% CI, 1.17 to 1.67; $p = 0.0003$ for OS).

However, many studies are old and no data are available as to whether there has been a change in the distribution of cancer within the breast over time in relation to tumour size, menopausal status and age. The present study was designed to address

this issue by studying two series of patients diagnosed in the Edinburgh Breast Unit over four decades apart.

2.2 Objective

The objectives were to determine:

(i) the site of cancer within the breast of two separate cohorts of women referred within the same geographical area but 40 years apart

and

(ii) whether site was related to other clinico-pathological features of the disease.

2.3 Materials and Methods

2.3.1 Patients

Two cohorts of women presenting with invasive breast cancer in the southeast of Scotland were studied: (i) 1,158 out of almost 1,400 patients diagnosed with breast cancer between 1957 and 1959, these are all patients who were referred to oncologist for further treatment, the site of the tumour's location was documented on the clinical notes in the patient's file, and (ii) 1,477 out of almost 1,600 patients diagnosed with breast cancer between 1997 and 1999 and referred to the Edinburgh Breast Unit.

The cases were selected on the basis of being able to retrieve the following details from files: confirmation of histological breast cancer, patient age and menopausal status, and tumour site, size and laterality. (Patients with bilateral tumours were excluded from this study.) These data were recorded prospectively on a proforma which was subsequently computerised.

2.3.2 Tumour location

Clinically the breast can be divided into 5 quadrants (upper outer, lower outer, upper inner, lower inner and central). This was utilised in this study to categorise tumour location, corresponding to upper outer quadrant (UOQ, Q1), lower outer quadrant (LOQ, Q2), upper inner quadrant (UIQ, Q3), lower inner quadrant (LIQ, Q4) and central (Q5). Big tumours which occupied more than one quadrant or small tumours located on the interface between two quadrants, e.g. at 12, 3, 6 and 9 o'clock, were classified in a single category (Q6).

2.3.3 Definition of menopausal status

Patients who were menstruating or were within 3 years of their last menstrual period were classified as premenopausal; those beyond 3 years of their last menopausal period were regarded as being postmenopausal [148]. In the cohort 1957-59, out of 1,158 patient 54 did not have their menopausal status recorded, this leaving 1,104 patients. In the cohort 1997-99, all 1,477 patients had their menopausal status recorded.

2.3.4 T stage

T stage of the cohort 1957-59 was available only for tumour pathological size; there were no records about the lymph nodes status and metastasis. As a result of this, only pathological tumour size was available for comparison between the two cohorts. Pathological tumour size in the cohort 1957-59 was recorded for 1,093 out of 1,158 (65 patients did not have their pathological size recorded). In the cohort 1997-99 all 1,447 patients had their pathological sizes recorded.

'Staging' takes into account the size of the tumour, whether lymph nodes are affected and whether the tumour has spread elsewhere. The most common system used to describe the stages of cancers is the American Joint Committee on Cancer (AJCC) TNM system [149]. This staging system classifies cancers based on their T, N, and M stages. The TNM system for staging is used all over the world [and separately assesses the tumour (T), nodes (N) and metastases (M).

Tumour (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor (this sometimes happens)

Tis: Pure carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget disease of the nipple with no associated tumour mass

T1: The tumour is no more than 2 centimeters (cm) across

T1 is further divided into 3 groups

- T1a the tumour is more than 0.1 cm but not more than 0.5 cm
- T1b the tumour is more than 0.5 cm but not more than 1 cm
- T1c the tumour is more than 1 cm but not more than 2 cm

T2: The tumour is more than 2 cm, but no more than 5 cm across

T3: The tumour is bigger than 5 cm across

T4: is divided into 4 groups

- T4a The tumour is fixed to the chest wall
- T4b The tumour is fixed to the skin
- T4c The tumour is fixed to both the skin and the chest wall
- T4d Inflammatory carcinoma - this is a cancer in which the overlying skin is red, swollen and painful to the touch

Nodes (N)

N0: normal and no enlarged lymph nodes in the axilla.

N1: lymph nodes in the axilla, which are mobile.

N2: fixed lymph nodes, suspicious of spread of the disease

N3: enlarged lymph nodes in the neck, or in the controlateral axilla

Metastases (M)

MX: Presence of distant spread (metastasis) cannot be assessed.

M0: No sign of cancer spread

M1: Cancer has spread to another part of the body, apart from the breast and lymph nodes under the arm, usually to the liver, lungs, bones and brain

2.3.5 Statistical Analysis

Comparisons were made using chi square test.

2.4 Results

2.4.1 Study groups

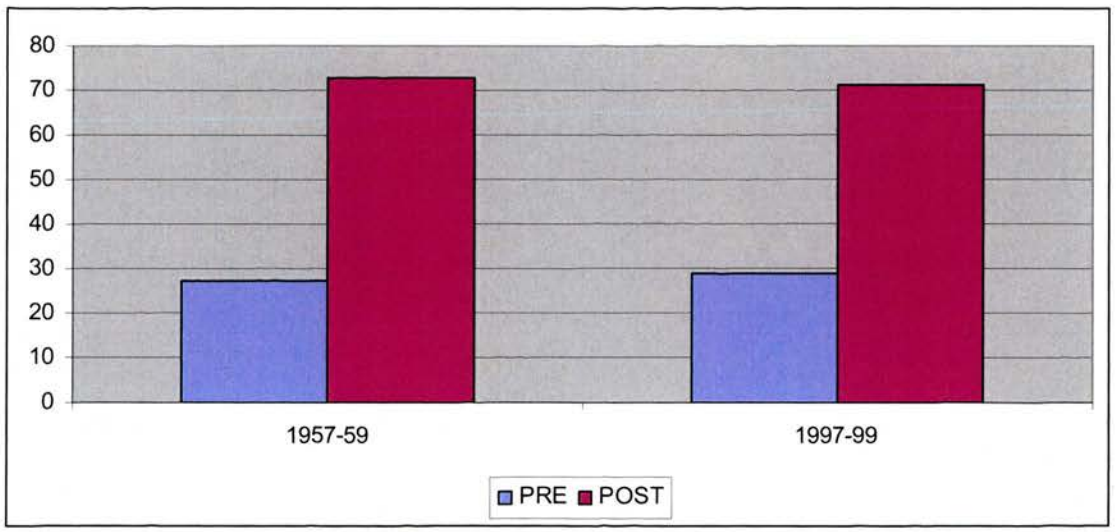
Both groups of patients were selected on the basis of being female, having a diagnosis of invasive carcinoma, unilaterality of disease and clear documentation of site within the breast of tumour. This provided 1,158 patients in 1957-59 (out of a total of 1,208 referred to the radiation oncology in Edinburgh) and 1,477 in 1997-1999 (out of almost 1,600 patients referred to the Edinburgh Breast Unit).

The demographic characteristics of patients and their tumours are shown in Table 1. The mean age at diagnosis for the 1957-59 cohort (57.7 years) was not significantly different from that of the 1997-99 cohort (61.6 years). The menopausal status was known on all patients in the 1997-99 cohort, but was missing on 54 cases in the earlier group. At diagnosis, 27.1% of women in the first cohort were premenopausal compared with 28.8% for the 1997-99 cohort. This change in proportion of premenopausal women was not statistically significant by Chi square test (χ^2=0.88, p=0.35) (Figure 1).

Table 1

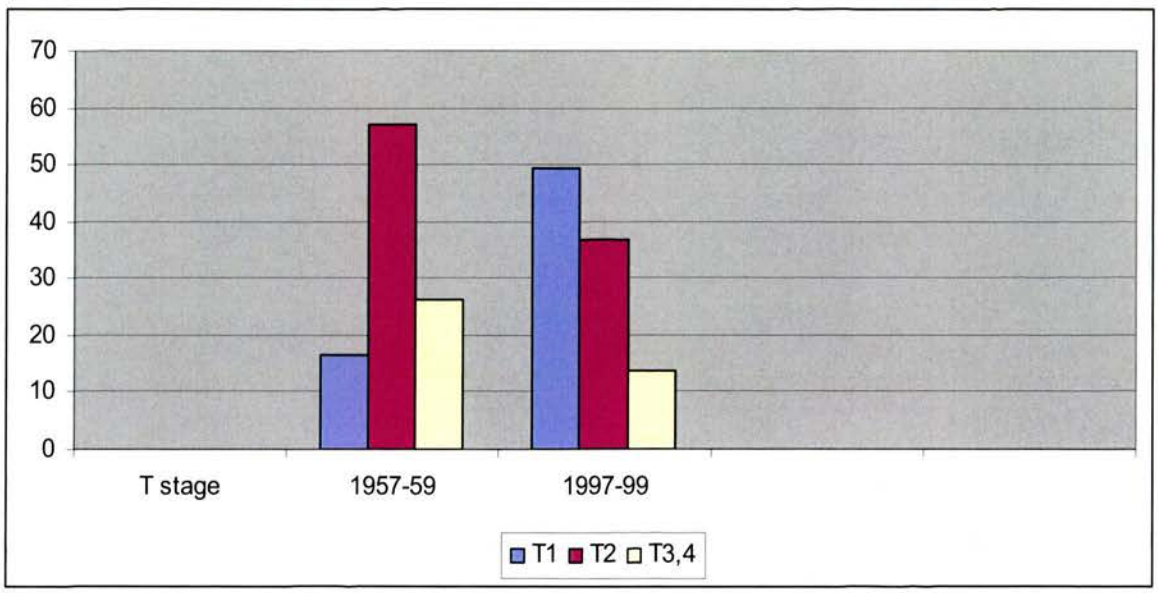
	1957-59	1997-99
Mean age (years)	57.7	61.6
Menopausal status		
Pre	299 (27.1%)	426 (28.8%)
Post	805 (72.9%)	1051 (71.2%)
T stage		
1	181 (16.6%)	729 (49.4%)
2	625 (57.2%)	545 (36.9%)
3/4	287 (26.2%)	203 (13.7%)
Laterality		
L	585 (50.5%)	753 (51%)
R	573 (49.5%)	724 (49%)

Figure 1: Menopausal status in two cohorts ($p = 0.35$)



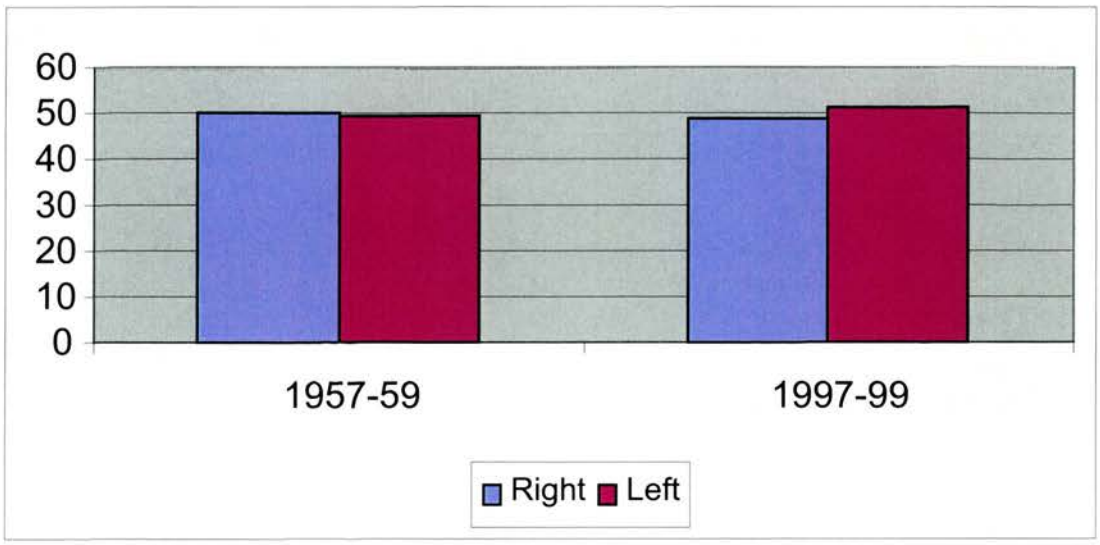
T stage (TNM classification was used as described in the materials and methods section) was known on all patients in the 1997-99 cohort, but was missing in 65 cases in the earlier cohort. In terms of T stage, there was a highly significant decrease, (chi-square = 24.6, $p<0.0001$) between 1957-59 and 1997-1999; 181 (16.5%) were T1, 625 (57.2%) T2, and 287 (26.2%) T3/4 patients in cohort 1957-59, as compared to 729 (49.3%) T1, 545 (36.8%) T2, and 203 (13.7%) T3/4 in cohort 1997-99 (Figure 2).

Figure 2: T stage in two cohorts ($p < 0.0001$)



In terms of cancer laterality, the tumour was equally likely to be in the left or right breast in both time periods (Figure 3).

Figure 3: Laterality in two cohorts



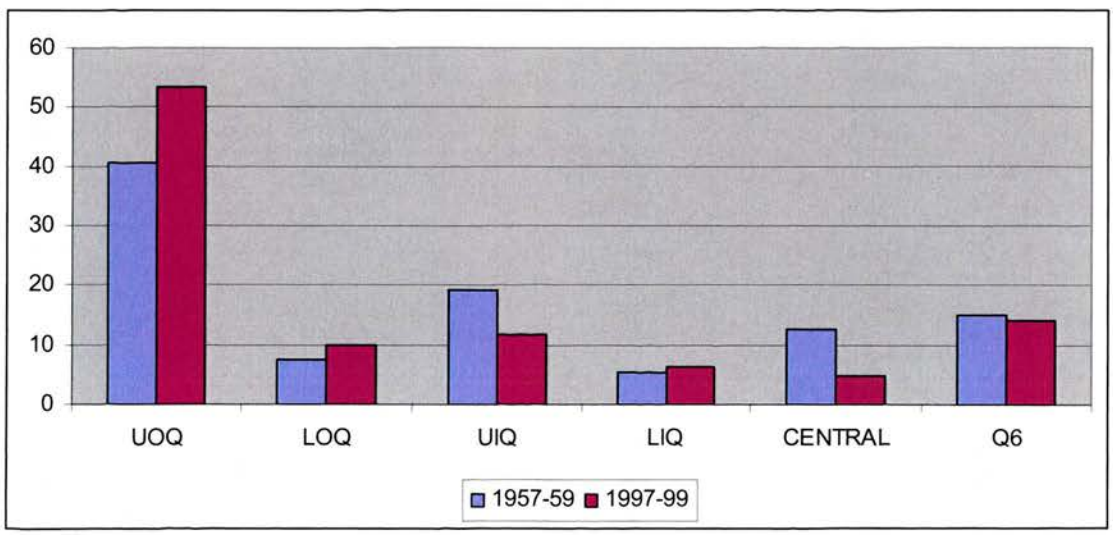
2.4.2 Tumour location in the breast

The sites of the tumours within the breast are summarized in Table 2 and shown in Figure 4 for both groups of women. The distribution in the breast was significantly different between 1957-59 and 1997-99 (χ^2 =100.288, p=0.0001).

Table 2: The site of breast cancer in different quadrants in two cohorts 1957-59 and 1997-99 (χ^2 =100.288, p = 0.0001)

Site	UOQ	LOQ	UIQ	LIQ	CENTRAL	Q6	TOTAL
1957-1959	469 (40.5%)	86 (7.4%)	221 (19.1%)	62 (5.4%)	145 (12.5%)	175 (15.1%)	**1158**
1997-1999	788 (53.4%)	147 (10%)	175 (11.8%)	91 (6.2%)	69 (4.7%)	207 (14.0%)	**1477**

Figure 4: Tumour sites in different quadrants in both cohorts, (χ^2 =100.288, p = 0.0001)



UOQ (upper outer quadrant)

The highest incidence of tumour was in the UOQ of the breast. Almost half the cases were found in this location irrespective of the time of diagnosis (Table 2). However, in the earlier patient cohort the incidence was 40.5% (469 of 1,158), whereas in the more recent cohort it was 53.4% (788 of 1,477). This increase in proportion was statistically significant (χ^2=42.45, p<0.0001).

LOQ (lower outer quadrant)

The incidence of tumours in the lower outer quadrant was low but increased between 1957-59 and 1997-99, from 7.4% to 10% respectively. This difference was statistically significant (χ^2=4.83, p=0.028).

UIQ (upper inner quadrant)

In contrast to the upper and lower outer quadrants, the upper inner quadrants decreased in incidence of tumours from 19.1% in the 1957-59 cohort to11.8% in the 1997-99 cohort. This difference was highly statistically significant (χ^2=26.05, p<0.0001).

LIQ (lower inner quadrant)

The incidence of tumours in this site was similar in both groups (5.4% and 6.2% respectively) and the difference between the groups was not statistically significant (χ^2=0.632, p=0.43).

Central

Similar to upper inner quadrant, and unlike the upper and lower outer quadrants, the central location decreased in the incidence of tumours from 12.5% in the 1957-59 cohort to 4.7% in the 1997-99 cohort. This difference was statistically highly significant (χ^2=40.88, p<0.0001).

Q6

This category showed a reduction in incidence from 15.1% in the 1957-99 cohort to 14% in the 1997-99 cohort and the difference was highly statistically significant (χ^2=23.38, p<0.0001).

2.4.3 Location of tumour in the breast according to T stage

Because there were statistically significant differences in the patients cohorts with regard to T stage it was of interest to determine whether this factor influenced changes in tumour location with time. These data are shown in Table 3 and illustrated in Figures 5, 6 and 7.

Table 3: The incidence of tumours in the breast zones in each T stage category

	UOQ	LOQ	UIQ	LIQ	CENTRE	Q6	TOTAL
T1							
1957-1959	75 (41.4%)	24 (13.3%)	43 (23.8%)	18 (9.9%)	13 (7.2%)	8 (4.4%)	**181** (16.6%)
1997-1999	380 (52..1%)	74 (10.2%)	87 (11.9%)	53 (7.3%)	33 (4.5%)	102 (14.0%)	**729** (49.4%)
Stats overall comparison χ^2=33.15, p<0.0001							
T2							
1957-1959	289 (46.2%)	43 (6.9%)	134 (21.4%)	36 (5.8%)	70 (11.2%)	53 (8.5%)	**625** (57.2%)
1997-1999	290 (53.2%)	50 (9.2%)	70 (12.8%)	29 (5.3%)	17 (3.1%)	89 (16.3%)	**545** (36.9%)
Stats overall comparison χ^2=67.47, p<0.0001							
T3/4							
1957-1959	81 (28.2%)	14 (4.9%)	32 (11.1%)	6 (2.1%)	46 (16.0%)	108 (37.6%)	**287** (26.2%)
1997-1999	118 (58.1%)	23 (11.3%)	18 (8.8%)	9 (4.4%)	19 (9.3%)	16 (7.8%)	**203** (13.7%)
Stats overall comparison χ^2=81.04, p<0.0001							

Figure 5: T1 in different quadrants in both cohorts

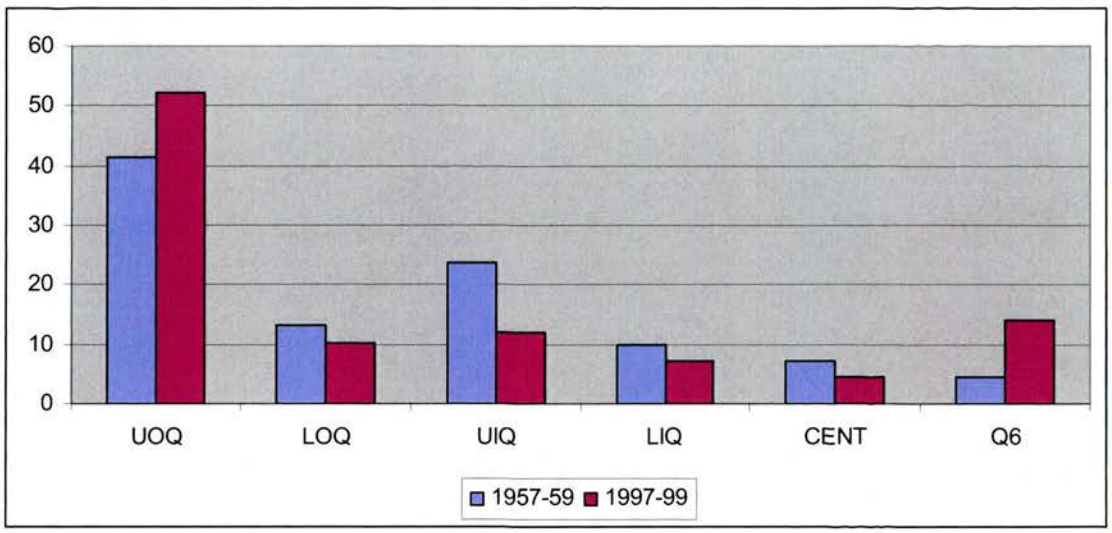


Figure 6: T2 in different quadrants in both cohorts

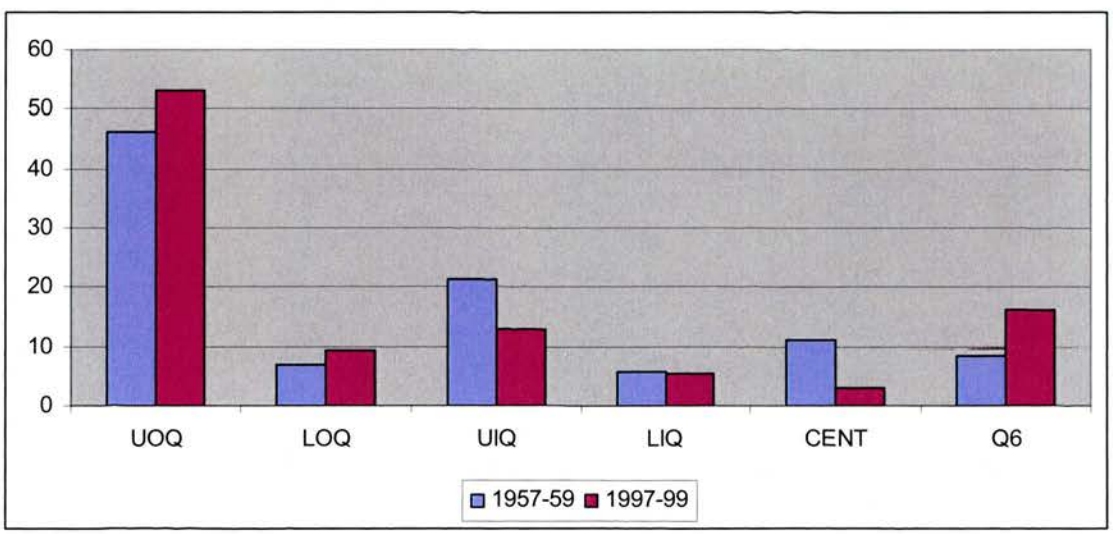
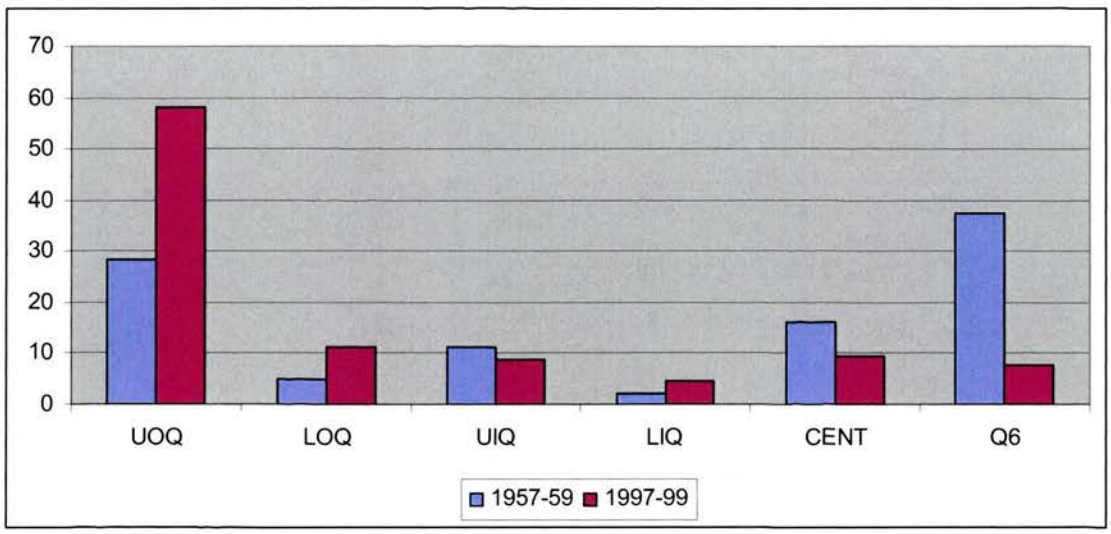


Figure 7: T3/4 in different quadrants in both cohorts



The difference in tumour location between 1957-59 and 1997-99 was apparent in all T stages, the difference being $p<0.0001$ in all cases. In terms of individual quadrants, consistent statistical significances were seen for each T stage for UOQ. The increased incidence in UOQ tumours over time is therefore unlikely to be a reflection of decreased size.

Where statistically significant differences were apparent between time groups for other zones, similar trends were also observed after subdivision into T stage; some did not reach statistical significance, probably on account of the small number of cases. The Q6 zone was unusual in that there was an increasing incidence in 1997-99 in T1 and T2 and a statistically significant decrease with T3/4.

2.5 Discussion

The present study has shown that over the last four decades there has not been an apparent change in menopausal status or in the laterality of patients with breast cancer, which is conflicting with other results, but there were significant changes for the size and distribution of breast cancer. It is important to consider the possible reason for these changes.

Thus, even if the observations are specific to Edinburgh, the characteristics of patients and tumours in this location have changed. It is possible that the difference results from the selection process used to identify patients during the second time period, but the distribution of cancers right versus left and menopausal status did not change and there is no reason why patients with breast cancer or those with UOQ lesion should have had changed incidence. This result is different compared to other published studies mentioned in the introduction.

Whilst the initiation of the screening programme in Edinburgh in 1991 will have had an impact on the population of women presenting with breast cancer, it is more likely to have reduced the proportion of premenopausal women, screening being offered to mainly postmenopausal women.

The most significant difference in the cancers between the cohorts was the increase in tumour size. Similar changes over time have been previously reported. This is likely to be in large part because of better education with increasing breast awareness and the introduction of the screening programme in Edinburgh in 1991.

The present study has confirmed previously reported findings that the distribution of breast cancer is not even throughout the breast but is higher in the upper outer quadrant (UOQ).

The study has also demonstrated that the preponderance of cancer in the upper outer quadrant is increasing with time. In the most recent time period almost half of cases were found in the UOQ irrespective of the laterality of the disease. The increases trend was significant ($p<0.0001$). There was an increase in the likelihood of finding a cancer in the lower outer quadrant (LOQ). The increased incidence in these quadrants was particularly seen in premenopausal women but was apparent in each T stage, unlike another study where there was increment in all quadrants.

The incidence of UOQ tumours was higher in premenopausal women in both cohorts ($p<0.0001$). The reason for the higher incidence of breast cancer at this site is ascribed to a greater proportion of breast tissue in the upper outer quadrant [124] and some changes in lifestyle [138].

In this study the change in the quadrant was correlated to the size of the tumour and the menopausal status, this will give a strong result with regards to bias with the site of the tumour in the quadrant. No similar study was done previously comparing the quadrants and the size.

The ability to reduce breast tumour growth through manipulation of oestrogen action has played a central role in the endocrine therapy of breast cancer [150], but little consideration has been given to the potential interaction of the presence of oestrogenic chemicals in the human breast on the effectiveness of this therapy in individual patients.
Interestingly, the UOQ is not only the most common site of the tumour in cancer but also of the abnormalities in benign breast conditions, including fibroadenoma, breast cysts [129], and phyllodes tumour [130].

Explanations for an increase of tumours in the upper outer quadrant include the possibility that agents administered topically to the axilla might gain access to the breast and be responsible for the initiation/promotion of tumours at that site. Interestingly compounds in deodorants, such as parabens, have been reported to

have the ability to penetrate the skin and have oestrogenic activity [151]. Whether this might promote tumour growth remains a matter of conjecture.

Since antiperspirants act by blocking sweat ducts [152], and breast cysts result from blocked breast ducts [124], it is possible that breast cysts could also arise from repetitive trauma to the ducts in this area. Studies of the relation between cysts and breast cancer have conflicting results. Some studies showed women with breast cysts are at an increased risk of breast cancer, especially at younger ages [153, 154].

Phytoestrogens are used increasingly in cosmetics designed for application around the human breast. There is an increasing trend towards addition of Aloe Vera into personal care products, and the constituent anthraquinones are known to possess oestrogenic properties [155].

Cosmetic chemicals such as aluminium salts [156], cyclosiloxanes and triclosan are already known to have DNA damaging properties as well as oestrogenic activity [157, 158]. The alkyl esters of p-hydroxybenzoic acid (parabens) are added in concentrations of up to 0.8% as preservatives to thousands of cosmetic products, which mimic oestrogen in breast tissue [158] and have been detected in human breast tumour tissue at an average concentration of 20 ng/g tissue [159].

The constant use of bras (particularly of under-wired which constricts breast tissue and lymphatics mostly in the outer quadrants by the very nature of its design) for long periods might influence lymphatic flow from the breast, this might be a cofactor with other factors in traumatizing tissues in the UOQ of the breast where the wire has the most pressure point.

Axillary hair is now frequently removed by different means and is currently performed more frequently than was done four decades ago. This potentially causes repetitive trauma to the axilla and neighbouring outer quadrants.

The accepted explanation for the disproportionate incidence of breast cancer in the UOQ of the breast is that this region of the breast contains a greater proportion of the epithelial tissue [143] which is the target site for breast cancer. However, evidence for this explanation is lacking and seems to be anecdotal in origin.

If this trend to increasing incidence of breast cancer in the UOQ is a function of time and is not a reflection of different study populations, then this would question the explanation for high incidence of breast cancer in the UOQ as being due solely to the presence of more epithelial tissue in that region. However, further studies need to be done to assess the cause of this disproportion especially for epidemiology prognosis.

Other epidemiological factors which may have changed between the two time cohorts and which may influence the risk of breast cancer include the length of pill usage, use of HRT, late first pregnancy, number of offspring/family size and long gap between pregnancies, alcohol and cigarette smoking. There is no obvious reason why these particular factors should influence tumour location, but it might influence breast cancer frequency and tumour size. Further studies need to be carried out to determine what might be the cause of this change in the distribution of breast cancer.

It should also be noted that changes over time in breast cancer do not only affect location. For example, there is some circumstantial evidence that temporal changes may be occurring in laterality. Many studies indicate that the left breast is more prone to development of cancer than the right breast in both female [124, 134, 135, 141, 142, 160] and male [141, 140] breast cancer. However, in a more recent American publication describing patients studied between 1973 and 1998, the numbers of right-sided and left-sided were roughly equal [161]. Interestingly the most common location for tumours was the upper outer quadrant of the breast. The stage and histology of breast cancer has also changed. As was also shown in the present study, more early breast cancer is being seen now as compared with in the past [162]. Similarly, while ductal carcinoma incidence rates remained essentially constant from 1987-1999, lobular carcinoma rates increased steadily [163, 164]. This may be because

HRT use has increased steadily from the 1970s to the 1990s [165-169]. Beyond their aetiologic importance these results also have clinical significance because ILC and IDC have different clinical features. For example, ILC is more likely to be hormone receptor–positive [170] and to have a better prognosis than IDC [171].

CHAPTER 3

SOCIOECONOMIC STATUS AND PROGNOSIS/ OUTCOME OF BREAST CANCER PATIENTS

3.1 Introduction

There is evidence that socioeconomic status (SES) is associated with the natural history of breast cancer both in terms of risk to the disease and outcome of women with breast cancer. This is reviewed in the following sections.

3.1.1 Assessment of Socioeconomic Status

There is a long-standing awareness that poverty is associated with general risk of ill-health and outcome from disease. There has, however, been controversy as to how best to assess and quantify poverty/socioeconomic status [172, 173].

The debate has centred mainly on the validity of social classes as a general measure of relative affluence or poverty in a society where other correlates of poverty (such as unemployment, single parenthood and old age) are increasingly prevalent [174, 175]. Several different ways of combining variables have been developed as a means of categorising the populations of small geographically defined areas such as census enumeration districts, local government wards or postcode sectors [173, 176, 177]. All combine variables to generate a summary score, which hopefully reflects the socioeconomic status of a locality relative to the distribution of scores obtained for all localities and reflect a principal component of the full census dataset which describes a socioeconomic dimension in these data [178, 179].

Morris and Carstairs [178] restructured the distribution of deprivation scores for postcode sectors to create a categorical variable ranging from deprivation category (DEPCAT) 1 (the most affluent) to deprivation category 7 (the most deprived). The variables comprising the score vary according to different censuses but basically utilise measures associated with material resources, access to amenities and physical environment as applied to postcode sectors. For example in the 1981 census variables included overcrowding, male unemployment, low social class based on head of household and no car.

The frequency distribution of DEPCAT categories in Scotland for the 1981 and 1991 censuses are summarized in Table 4.

Table 4

	1981				**1991**			
DEPCAT	Population	%	Postcodes	%	Population	%	Postcodes	%
1	305,868	6.1	105	10.4	305,725	6.1	94	9.4
2	691,280	13.7	180	17.8	688,018	13.8	171	17.1
3	1,095,583	21.8	253	25	1,090,483	21.8	226	22.6
4	1,282,976	25.5	219	21.7	1,270,597	25.4	231	23.1
5	743,689	14.8	117	11.6	741,664	14.8	125	12.5
6	571,901	11.4	91	9	567,492	11.4	97	9.7
7	340,998	6.8	45	4.5	334,285	6.7	57	5.7
Total	**5,032,295**	**100**	**1,010**	**100**	**4,988,264**	**100**	**1,001**	**100**

(Table modified from Morris R, Carstairs V. *J Public Health Med* 1991;13:318-26)

3.1.2 Socioeconomic Status and Risk

There is evidence that degree of affluence influences chances of developing breast cancer. This is derived from two major sources – (i) the international distribution of the disease and (ii) the socioeconomic status within discrete populations. Both sets of data suggest that increased affluence is associated with increased risk and that socially deprived populations may be less vulnerable to the disease [180-186].

In terms of the influence of SES within individual international populations, data has been published from many different countries, including USA (where African American, Hispanic/Latina, Asian American/Pacific Islander and American Indian/Alaska Native women have lower incidence rates than Whites), Japan, Netherlands, Demark, Sweden and the UK (including Scotland).

Breast cancer incidence rates in Scottish women are rising in parallel across all socioeconomic categories and the incidence gap between deprived and affluent still remains [180].

For example, data on breast cancer incidence rates by deprivation quintile in Scotland 1991-2000 were analysed using linear regression. Incidence data for breast cancer incidence per 100,000 women (age-standardised to the European Standard Population) from 1991 to 2000 in each deprivation quintile of the Scottish population was obtained from the Information and Statistics Division of the Scottish Executive (ISD). Deprivation quintiles divide the Carstairs and Morris index - an index calculated for individual postcodes based on factors such as occupation of head of household - into five equal categories. Between 1991 and 2000, breast cancer incidence rates in Scotland continued to be lower with increasing deprivation. Linear regression reveals a significant rise in incidence over this period in all quintiles (except for quintile 2). In the most affluent the rise in incidence was of the magnitude of 1.9 cases per 100,000 per year, and in the most deprived 1.0 case per 100,000 per year. Interaction analysis revealed regression slopes to be parallel (p =

0.778), confirming that incidence rates are rising to the same degree in all deprivation categories [180].

The exact causes behind these observations are not fully defined and, indeed, it is likely that the differential effects may be multifactorial. However, amongst the reasons underlying the phenomenon include lifestyle factors such as diet, stress, reproductive and child-bearing parity, the use of oral contraceptives, HRT, radiation and environmental factors, but it cannot be excluded that the increased incidence in more affluent populations is due to more efficient diagnosis of the disease.

The study mentioned above [180] also examined other aetiological factors, such as first births at late maternal age, BMI trends (based on the Scottish Health Surveys) and breast screening uptake trends. Since the late 1980s, numbers of first birth in Scottish women aged 35-39 have risen dramatically (especially in the affluent), but numbers were stable before this. The prevalence of obesity and mean BMI has increased over time in all socioeconomic classes, but BMI continues to be higher in the deprived. Uptake of screening invitations has increased in all socioeconomic groups. It was therefore concluded that trends in late age at first pregnancy, prevalence of obesity and screening uptake do not fully explain the observed trends [180].

According to data from the NHIS, utilization of screening mammography has increased greatly among White and African American women of all ages since 1987. Among White women, the percentage of women aged 40 and older who reported having had a mammogram within the past 2 years increased from 30% in 1987 to 71% in 2003. Similarly, during 1987 to 2003, the prevalence of mammography usage among African American women increased from 24% to 70%, respectively. Although current overall usage of mammography is similar among White and African American women, usage remains lower in women of other racial and ethnic groups [117]. Women with less than a high school education, without health insurance coverage or who are recent immigrants to the United States are even less

likely to have had a recent mammogram. The results indicate social inequalities regarding awareness of the disease and/or access to early detection and this, in turn, might translate into a higher apparent risk in more affluent women.

3.1.3 SES and Prognosis/Outcome

The clinical behaviour of breast cancer is variable. Many patients survive for extended periods of time with minimum treatment, whereas others die relatively quickly despite the implementation of a combination of surgical, radiation and systemic therapy [187].

Socioeconomic status is a factor which has been suggested to influence prognosis. Women with breast cancer from lower socioeconomic groups have relatively lower survival than affluent women and this difference in outcomes seems independent of the measure of socioeconomic status used [188].

The quantitative effects of SES on outcome of breast cancer are best illustrated with examples. For example, in Finland the effect of social class on survival of female breast cancer patients was studied by linking the patient files of the Finnish Cancer Registry (FCR) with the information on patient's social status, obtained from the 1970 Population Census of Finland. The material consisted of 10,181 patients 25-69 years of age at diagnosis, whose cancer was diagnosed between 1971 and 1980. The classification of social class was based on occupation. Those in the lowest social class had about 1.3 times higher relative excess risk of dying than those in the highest social class.

Another study in the UK was carried out on 10,865 cases of breast cancer from the East Anglian Cancer Registry diagnosed between 1982 and 1993. It was estimated that the extent to which the differences in survival by socioeconomic status, measured by both occupational and area-based methods, could be explained by differences between socioeconomic groups in stage and morphological type of

tumour. In univariate survival analyses, lower social class (manual occupation) was associated with a relative hazard of 1.32 (95% CI 1.12-1.55) for death from breast cancer as underlying cause. Women resident in the most deprived area had a relative hazard of 1.21 (0.95-1.54) for death from breast cancer as underlying cause [189].

The clinical importance of this observation depends on the magnitude of the difference in survival. A recent review of cancer registration data from England and Wales indicated a difference of 5-10% both for absolute and relative survival between the affluent and deprived groups depending on the period of diagnosis [190].

A study performed in west Scotland on 1,361 women aged under 75 who had breast cancer diagnosed between 1980 and 1987 showed that there was no significant relation between socioeconomic deprivation and four pathological prognostic factors: 93 (32%) women in the most affluent group presented with tumours less than 20 mm in size compared with 91 (31%) women in the most deprived group; 152 (48%) of the most affluent group presented with negative nodes compared with 129 (46%) of the most deprived group; 23 (22%) of the most affluent group presented with grade I tumours compared with 12 (17%) of the most deprived group, and 142 (51%) of the most affluent group had a low oestrogen receptor concentration at presentation compared with 148 (52%) of the most deprived group. None of these differences was statistically significant and it was concluded that differences in survival from breast cancer by socioeconomic deprivation category could not be accounted for by differences in tumour stage [122].

In a study carried out in Scotland, differences in survival from breast cancer were compared between women resident in affluent and deprived areas. Two datasets relating to breast cancer patients in Scotland were analysed: (1) population-based cancer registry data; (2) a subset of cancer registration records supplemented by abstraction of prognostic variables (stage, node status, tumour size, oestrogen receptor (ER) status, type of surgery, use of radiotherapy and use of adjuvant systemic therapy) from medical records. The study was carried out on patients from

cancer registration data on 21,751 women aged under 85 years diagnosed with primary breast cancer between 1978 and 1987; and national clinical audit data on 2,035 women aged under 85 years diagnosed with primary breast cancer during 1987. Survival differences of 10% between affluent and deprived women were observed in both datasets, across all age groups.

In the audit dataset, the distribution of ER status varied by deprivation group (65% ER positive in affluent group v 48% ER positive in deprived group; under 65 age group). Women aged under 65 with non-metastatic disease were more likely to have breast conservation than a mastectomy if they were affluent (45%) than deprived (32%); the affluent were more likely to receive endocrine therapy (65%) than the deprived (50%). However, these factors accounted for about 20% of the observed difference in survival between women resident in affluent and deprived areas. They concluded that deprived women with breast cancer have poorer outcomes than affluent women, explained by deprived women having more ER negative tumours than affluent women [191].

In the Netherlands, a country characterized by good general access to health care services, the survival rates of patients with cancer by socioeconomic status (SES) has never been investigated. The association between socioeconomic status and survival from cancer of the lung (n = 4591), breast (n = 3928), colorectum (n = 3558), prostate (n = 1484), and stomach (n = 1455) was studied. A more favourable relative survival for patients living in high SES areas was found for those with cancer of the lung, breast, colorectum and prostate, whereas for those with stomach cancer, lower survival was found for patients living in high SES areas [192].

In a study from South Thames, Pollock et al [193] also showed a clear trend was observed in standardized mortality rates across deprivation tenths for three tumour sites (breast, lung and colorectal); mortality increased with deprivation. Significantly lower 5-year relative survival rates were found for breast and colorectal cancer patients in the most deprived groups. Breast cancer patients resident in the most

affluent tenth of enumeration districts had a 70% relative survival ratio compared with 57% in the most deprived tenth.

The underlying causes behind more socially deprived patients having poorer outcome may be multifactorial and may differ according to individual populations. However, amongst the reasons are (i) disease associated factors such as more advanced stage at presentation, higher histological grade, less ER positivity, (ii) lifestyle related risk factors for cancer such as smoking, nutritional habits, drinking habits and reproductive factors, which are prevalent in lower socioeconomic groups [194] and (iii) differences in management of disease such as inferior treatment and follow-up. The evidence for this is summarized below.

(i) disease associated factors

Extent of disease at the time of presentation has a major impact on prognosis [191], but equally women with the same treatment and clinical stage may survive for widely differing lengths of time.

Some studies have observed a positive relationship between social deprivation and more advanced stage of disease (and corresponding poorer outcome). For example, several Scottish studies attributed socioeconomic effects to differences in stage at presentation [186, 195] in that patients with cancer from deprived communities in Scotland appear to present with more advanced disease [121, 196].

A study was performed in west Scotland on 1,361 women aged under 75 who had breast cancer diagnosed between 1980 and 1987. It showed no significant relation between socioeconomic deprivation and four pathological prognostic factors: 93 (32%) women in the most affluent group presented with tumours less than 20 mm in size compared with 91 (31%) women in the most deprived group; 152 (48%) of the most affluent group presented with negative nodes compared with 129 (46%) of the most deprived group; 23 (22%) of the most affluent group presented with grade I

tumours compared with 12 (17%) of the most deprived group, and 142 (51%) of the most affluent group had a low oestrogen receptor concentration at presentation compared with 148 (52%) of the most deprived group.

A Swedish study detected significant social differences ($p < 0.01$) in distribution of clinical stage as well as in total and stage-specific survival. High income, more skilled work and a high level of education were all associated with clinically less advanced tumours and hence better survival. However, social gradients were most obvious in mortality associated with non-breast cancer events [197].

In a study from South Thames [198], irrespective of age, women in the most deprived category had a 35% greater hazard of death than women from the most affluent areas after adjustment for stage at diagnosis, morphological type and type of treatment. However, in younger women (30-64 years) the survival gradient by deprivation category cannot be explained by these prognostic factors. In older women (65-99 years), part of the unadjusted gradient in survival can be explained by differences in the stage of disease: older women in the most deprived category were more often diagnosed with advanced disease. Other factors, so far unidentified, are responsible for the gradient in breast cancer survival by deprivation category. The potential effect on breast cancer mortality of eliminating the gradient in survival by deprivation category is substantial (7.4%). In women aged 30-64 years, 10% of all deaths within 5 years might be avoidable, while in older women this figure is 5.8%. In a study from the Netherlands, the socioeconomic variation in survival of patients with breast cancer could be ascribed mainly to differences in the percentage of patients diagnosed with a metastasis [199].

Factors that may contribute to later stage at diagnosis among minority women are less frequent mammography [200], delays from time of abnormal mammographic findings to diagnostic confirmation and treatment [201], more limited access to health care [202], and more aggressive tumour characteristics [203].

Oestrogen receptor positive tumours generally have a better prognosis than oestrogen receptor negative tumours [205-207]. It is therefore interesting that socially deprived women have been reported to have a higher incidence of ER-ve tumours than affluent women [190, 208]. However, in contrast, in west Scotland 51% of the most affluent group of patients had tumours with a low oestrogen receptor concentration at presentation compared with 52% of the most deprived group. However, the difference was not statistically significant and it was concluded that differences in survival from breast cancer by socioeconomic deprivation category could not be accounted for by differences in tumour ER [122].

Another study in Scotland suggested that level of social deprivation is associated with oestrogen receptor status; the distribution of ER status varied by deprivation group (65% ER positive in affluent group v 48% ER positive in deprived group; under 65 age group) [191].

(ii) host factors

Whilst there is no direct evidence for general differences in natural hormone levels between women of different socioeconomic status, other influences which may vary with social status such as body weight, exercise, self-examination and diet can affect production and circulating level of oestrogens [209-212]. Nevertheless body mass index may influence survival of breast cancer patients [213].

Although race does not appear to be immediately associated with breast cancer outcome after adjusting for SES and other confounding factors such as demographic and disease characteristics [214], another study stated that "poor persons, regardless of their race, are likely to have undesirable cancer outcomes" [202].

The possibility exists therefore that other factors inherently present in the lifestyle/ environment of women of low socioeconomic status are directly affecting the history of the breast cancer [215-217], such as smoking, nutritional habits, drinking habits and reproductive factors, which are prevalent in lower socioeconomic groups [218].

(iii) differences in management of disease

It is possible that the difference between socially deprived and affluent patients reside not in the disease itself but in the efficiency of diagnosis and the nature of treatment and follow-up which the groups receive.

In terms of diagnosis, it has been shown that socioeconomic disparities in breast cancer survival prevail even in this relatively homogenous society, offering outreach mammography and standardised treatment regimens in a tax-funded health care system [208].

During the interval 1995 to 2001, the proportion of cases diagnosed at regional and distant stages combined was 43% among African American women, 43% in American Indian/Alaska Natives, 42% in Hispanic/Latinas, 34% in Asian Americans/Pacific Islanders and 33% among White women. Factors that may contribute to later stage at diagnosis among minority women are less frequent mammography [200] and delays from time of abnormal mammographic findings to diagnostic confirmation and treatment [201].

It has also been postulated that socioeconomic differences may be related to treatment, those who are more socially aware being more likely to be referred to specialist cancer centres [219].

Population-based statistics in the United States indicate that overall age-adjusted breast cancer mortality rates are higher among black women than white women, and the disparity is increasing. The aetiology of the widening racial disparity is poorly

understood. However, these trends might be attributable to disparities in health care quality or access, different responses to newer medical interventions, or alterations in risk factors (such as nutrition, physical activity, obesity, or childbearing practices) [202, 219-221].

One study in the US, looking at disparities between women of different socioeconomic status, showed than women without private health insurance were less likely than privately insured women to be screened for breast cancer and their treatment may differ after cancer is diagnosed. In this study they addressed two related questions: Do uninsured patients and those covered by Medicaid have more advanced breast cancer than privately insured patients when the disease is initially diagnosed? And, for each stage of disease, do uninsured patients and patients covered by Medicaid die sooner after breast cancer is diagnosed than privately insured patients? The study was performed on 4,675 women, aged 35-64 years, in whom invasive breast cancer was diagnosed from 1985-1987. The stage of disease and stage-specific survival among women with private insurance, no insurance, and Medicaid coverage through June 1992 was compared. The adjusted risk of death for these groups was estimated, using proportional-hazards regression analysis to control for age, race, marital status, household income, coexisting diagnoses and disease stage. The result was uninsured patients and those covered by Medicaid presented with more advanced disease than did privately insured patients ($p<0.001$ and $p=0.01$, respectively). Survival was worse for uninsured patients and those with Medicaid coverage than for privately insured patients with local disease ($p<0.001$ for both comparisons) and regional disease ($p<0.001$ for both comparisons), but not distant metastases. The adjusted risk of death was 49% higher (95% confidence interval, 20-84%) for uninsured patients and 40% higher (95% confidence interval, 4 - 89%) for Medicaid patients than for privately insured patients during the 54 to 89 months after diagnosis. It was concluded that the more frequent adverse outcomes of breast cancer among women without private health insurance suggest that such women would benefit from improved access to screening and optimal therapy [219].

In the above study the authors found that, compared with white women, African-American women were 53% more likely than white women to be diagnosed with later-stage disease, 26% less likely to receive radiation after breast-conserving surgery, more than twice as likely to receive no surgery, and 39% more likely to die. But when the authors adjusted their data to account for race and socioeconomic factors, differences in these outcomes, except for choice of surgery, nearly vanished. Compared with white women, African-American women were 62% more likely to have no surgery. If the African-American women had surgery, they were 63% more likely to receive breast-conserving surgery.

Women insured by Medicaid were 41% more likely to be diagnosed with late-stage breast cancer, 44% less likely to receive radiation after breast-conserving surgery, and three times more likely to die than women not insured by Medicaid. The authors concluded that, "poor persons, regardless of their race, are likely to have undesirable cancer outcomes. This finding should challenge the research and policy communities to provide remedies for reducing these disparities." [202, 222].

Socioeconomic variation in survival from a number of common cancer sites exists in the Netherlands, despite the fairly equal access to health care services for different socioeconomic groups [192].

A different study investigated the relationship between socioeconomic status (SES) and the use of intentionally reduced doses of chemotherapy in the adjuvant treatment of breast cancer. Patients with breast cancer treated with a standard chemotherapy regimen (n = 764) were enrolled in a prospective registry after signing informed consent. Detailed information was collected on patient, disease and treatment, including chemotherapy doses. Zip code level data on median household income, proportion of people living below the poverty level, and educational attainment were obtained from the US Census. Doses for the first cycle of chemotherapy lower than 85% of standard were considered to be reduced. Univariate analyses and multivariate logistic regression were performed to identify

factors associated with the use of reduced first cycle doses. The result showed individual education attainment, zip code SES measures, body mass index and geographic region were all significantly associated with receipt of intentionally reduced doses of chemotherapy. In multivariate analysis, controlling for geography, factors independently associated with reduced doses were obesity (odds ratio [OR], 2.47; 95% CI, 1.36 to 4.51), severe obesity (OR, 4.04; 95% CI, 1.46 to 11.19), and education less than high school (OR, 3.07; 95% CI, 1.57 to 5.99) and it was concluded that social disparities in breast cancer outcome is in part the result of lower quality chemotherapy doses in the adjuvant treatment of breast cancer [223].

The relation of economic status to survival was studied for 39 kinds of cancer representing all types for which 60 or more indigent patients were seen in the University of Iowa Hospital for primary care during the years 1940-1969. For every type the indigent patients had poorer survival than non-indigent patients. Quality of care would be eliminated as a major variable since a second group of "ward" patients of higher economic status was available for comparison and the differences were substantially greater between the two groups of teaching patients than between the "clinic pay" and "private" patients. Age differences and differences in stage of disease accounted for less than half of the survival deficits in the indigents. The two important problems were high mortality from causes other than cancer and excess cancer mortality not accounted for by stage differences, particularly among patients who should have had 5-year survival rates between 40-70%. In these patients cancer recurred more often and earlier among the indigent. Postulate host differences associated with poverty could also account for much of the observed Black-White differences as well as some international differences in cancer survival rates [194, 224, 225].

Sainsbury et al [226] used cancer-registry data from 12,861 patients with breast cancer treated in Yorkshire, UK, between 1979 and 1988, and found that patients of surgeons with higher rates of usage of chemotherapy and hormone therapy (regional mean usage 9.3%, range 0-46%) had prolonged survival. There was considerable

variation in survival of breast cancer patients between surgeons, but their rate of use of chemotherapy and hormone therapy explained about 26% of this survival variation. Had the practice of the surgeons with the better outcomes been used by all treating clinicians, 5-year survival would have increased by about 4-5%. Examination of differences in survival as a function of consultant caseload demonstrated poorer results amongst those surgeons treating less than 30 new cases of breast cancer per year (risk ratio [95% CI] for treating >30 compared with <10 = 0.85 [0.77-0.93]).

Miscellaneous

A study held in the UK examined national trends and socioeconomic inequalities in cancer survival during the 1990s using population-based data on 2.2 million patients who were diagnosed with one of the 20 most common cancers between 1986 and 1999 and followed up to 2001. Survival for most cancers in both sexes continued to improve during the 1990s. The deprivation gap in survival between rich and poor was wider for patients diagnosed in the late 1990s than in the late 1980s. Increases in cancer survival in England and Wales during the 1990s are shown to be significantly associated with a widening deprivation gap in survival [227].

Considering that five year observed survival for women with breast cancer in Scotland improved by just six percentage points (from 50% to 56%) in the 16 years from 1970 to 1985 [120], the potential benefit of understanding and remedying the difference between socioeconomic groups is substantial.

Objectives

The objectives of this study were to (i) quantify and investigate differences in survival from breast cancer between women resident in affluent and deprived areas of the southeast of Scotland, and (ii) define the contribution of underlying factors of this variation.

3.2 Materials and Methods

3.2.1 General Approach

The general approach was to study a large cohort of patients who were referred to the Edinburgh Breast Unit between 1985 and 1993 (and therefore have already at least 5 years follow-up). These patients were (i) staged and treated by standard Unit policy, (ii) stratified into different socioeconomic groups according to Carstairs Index [178] and (iii) were available for extended follow-up. Correlations therefore could be made between socioeconomic status and known prognostic factors, time to recurrence and survival.

Patient database

Cases for this study were derived from a single unit (Edinburgh Breast Unit) which is the major referral centre for the southeast of Scotland and sees over 90% of patients from this area. Patients with histologically-proven breast cancer diagnosed between 1985 and 1993 were identified. The present study was part of a wider investigation in which tumour biology was being investigated. An additional recruitment criterion was the need for fresh cancer tissue for analysis (but these analyses were not part of the present study). The other reason for inclusion of these patients, apart from being diagnosed with breast cancer and the availability of the tumour tissue (stored in the Edinburgh Breast Unit bank), was access to the files with complete needed information. ie address at diagnoses, full pathological information (lymph nodes status, ER status, menopausal status, and pathological tumour size), and regular follow up for at least 5 years. Patients' files which did not have sufficient information or patients with small tumours where tissue was not enough to store in the bank were excluded. All patients with detailed information available in the files and the availability of fresh tissues in the store were included in the study - this made the total number of patients small.

A total number of 502 patients were studied and the following details were documented: the patient's postcode at time of diagnosis, age, menstrual status, tumour size, lymph node status, presence/absence of distant metastasis and ER status of the primary tumour. All patients were routinely followed up and information on date of recurrence, disease free survival, overall survival and cause and date of death recorded (the minimum follow up was 262 weeks. Survival analysis was based on deaths from all causes due to lack of information on cause of death.

As a consequence, elderly patients with more advanced disease and small tumours may be under-represented in these studies. However, these categories were not totally absent and, when analysed as markers of prognosis or correlated with other established parameters, have yielded results concordant with published literature embracing higher numbers of cases and representative populations of patients.

Lymph node status

Lymph node status was determined pathologically by examination of nodes derived from either full axillary dissection or axillary sampling (if possible, by identification of 4-6 lymph nodes). The cases were subdivided according to whether no involved lymph nodes were found (negative) or whether one or more were found to be involved with cancer (positive).

Oestrogen receptor status

Oestrogen receptors were measured either by ligand binding or immumohistochemistry as described by Jennet et al [228]. Tumours were scored as positive if the ER measurement was >20 fmol/mg cytosolic protein or ≥10% staining and negative if below these cut-offs.

Menopausal status

Patients who were menstruating or were within 3 years of their last menstrual period were classified as premenopausal; those beyond 3 years of their last menopausal period were regarded as being postmenopausal.

Clinical T stage

This was adapted from that defined by TNM criteria [149]. The staging of breast cancer involves clinical, pathological and radiological data. A commonly used classification system is the TNM (Tumour, Nodes, Metastases) system which stage a tumour according to the size and extent of local spread of the tumour, the presence of lymph node metastases, and the presence of distance metastases, usually to the liver, bone, lung and brain.

In the UK the majority of breast cancer cases are early breast cancers, at diagnosis, usually at TNM staging T1 and T2.

Deprivation score (Carstairs Index)

The method of Carstairs and Morris was used to derive a deprivation score. This measure is based on the postcode of residence at diagnosis. As discussed in the introduction, the Carstairs formula utilized census data. Both deprivation criteria and postcode score vary between different censuses. The time period of patient recruitment (1985-1993) encompasses two censuses (1981 and 1991). Patients who were diagnosed before 15.6.85 were therefore classified under Census 1981, and those after this date were classified under 1991.

The deprivation scores for postcode sectors create a categorical variable ranging from deprivation category 1 (the most affluent) to deprivation category 7 (the most deprived). Because of relatively small numbers in some of the categories, in the

present study groups have been combined to yield zones in which zone A comprises categories 1 and 2 (the most affluent/least deprived), zone B comprises DEPCAT category 3 alone, zone C comprising category 4 alone, and zone D comprising DEPCAT categories 5, 6 and 7 (the least affluent/most deprived).

Data Analysis

Clinical data were related to SES status by chi square analysis. Clinical factors and SES status were examined individually to investigate whether any related to outcome measures (recurrence and survival at 5 and 10 years by chi-squared testing and all outcome data by Kaplan-Meier). Survival analysis was based on deaths from all causes due to lack of information on cause of death. For the survival analysis, patients were censored at the date they were last known to be alive. For the analysis of relapse, patients were censored at the date when they were last known to be alive and disease free or at the date when they died free of disease.

Cox's proportional hazards modeling was applied to the audit data to examine the effect of introducing other variables into the model on the relative hazard ratios for the intermediate and most deprived groups relative to the affluent group. The possible prognostic variables for survival which were considered were: Year treated, Age, Menopausal status, T, ER, Clinical size, Number of +ve nodes, Zone (socio-economic status).

3.3 Results

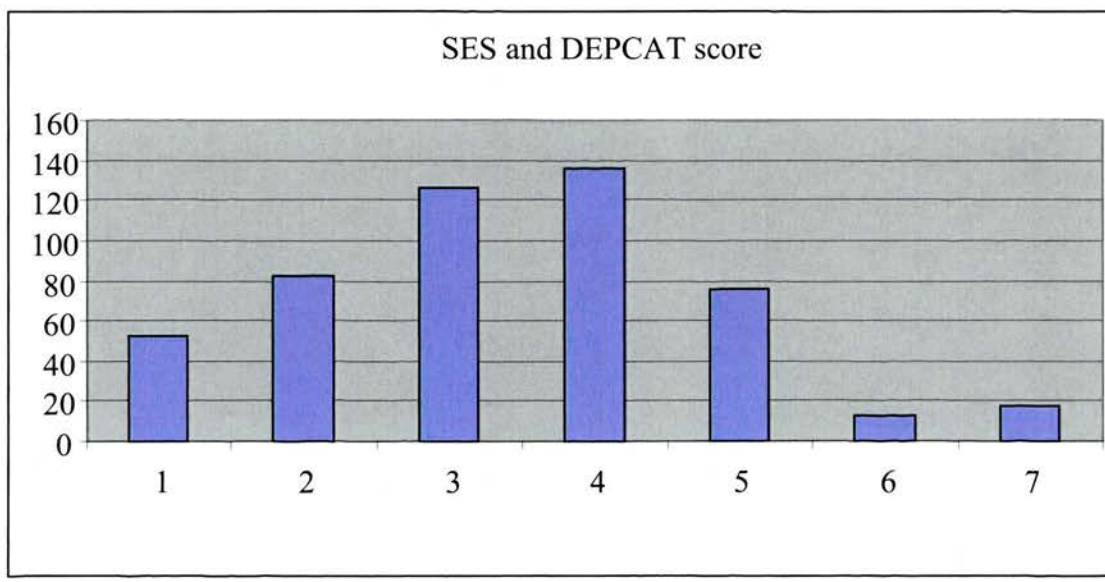
3.3.1 Subdivision of cases by socioeconomic status

In all, 502 patients diagnosed with invasive breast cancer between 1985 and 1993 were included in the study. These were subdivided according to Carstairs Index into different socioeconomic groupings on the basis of their postcode as described in the Methods section. The number of patients in each of the seven DEPCAT is shown in Table 5 and the distribution within the groups shown in Figure 8. This shows a bell shaped curve with the majority of cases (52%) in DEPCAT 3 and 4.

Table 5: distribution of cases by DEPCAT score

DEPCAT score	1	2	3	4	5	6	7	TOTAL
Number patients	52	82	126	136	76	13	17	502
Percent	10.4	16.3	25.1	27.1	15.1	2.6	3.4	100

Figure 8: distribution of cases by SES DEPCAT

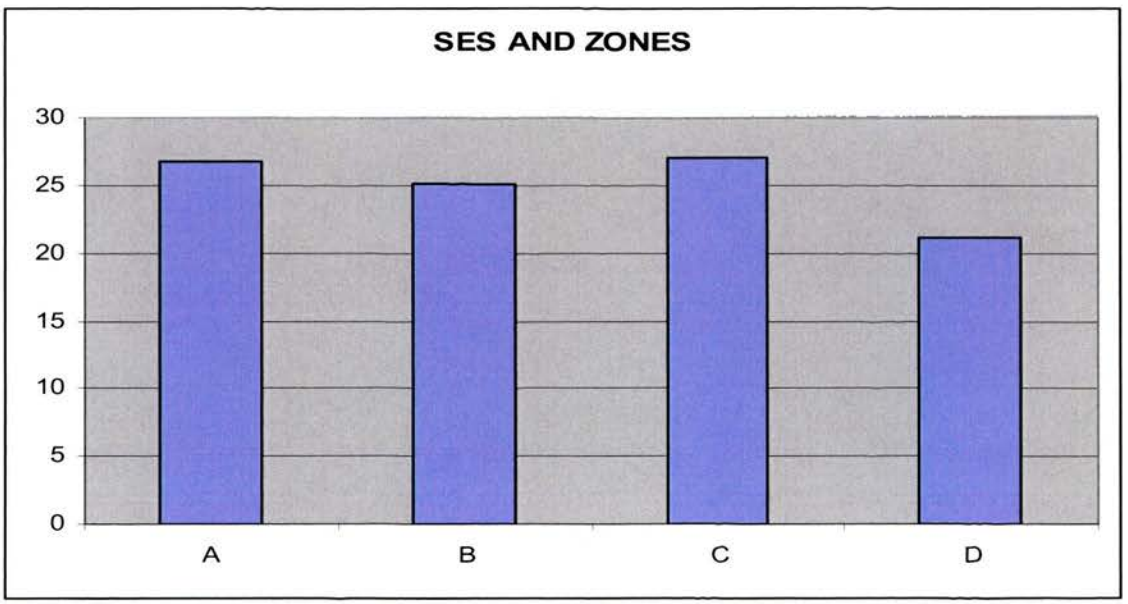


Because of the relatively small number of cases in DEPCAT 1, 2, 5, 6, and 7, for certain analyses DEPCAT 1 and 2 have been grouped together (zonal group A - 26% and the most affluent) as have 5, 6 and 7 DEPCAT (zonal group D - 21% most deprived) to create categories with similar numbers to those in DEPCAT 3 (25.1% zonal group B) and DEPCAT 4 (27.1% zonal group C) as is shown in Table 6 and Figure 9. Two sets of statistical tests were performed according to the seven DEPCAT or the four zonal groups. Additionally, trends across 7 DEPCAT levels have been analyzed but in order to identify a group of socially deprived cases DEPCAT 6 and 7 have been combined and compared against 1-3, 4-5 categories with power calculations based on n=260, 212 and 30 of 502 patients.

Table 6: distribution of cases by zones

Zones	A	B	C	D	TOTAL
Number patients	134	126	136	106	502
Percent	26.7	25.1	27.1	21.1	100

Figure 9: distribution of SES into zones



3.3.2 Survival

Survival was assessed by multiple criteria: A - according to whether patients were alive or dead at 5 years; B - whether patients were alive or dead at 10 years and C - by Kaplan-Meier survival curves taking the time of death as an incident point and as a continuous variable.

A – alive or dead at 5 years

The number of patients dead at 5 years was 127 (25.3%). The survival figures at 5 years subdivided according to socioeconomic status are summarised in Table 7 and shown diagrammatically in Figure 10. The percentage of women dying at 5 years varied between the groups - being lowest in DEPCAT 3 (18.3%) and highest in DEPCAT 6 (38.5%). Since the groups are graded progressively according to SES, it was appropriate to apply χ^2 analysis for trend to the data. This produced a χ^2 value of 4.96 and a significant p value of 0.026. Despite the p value being significant, it should be noted that there was not a simple increase in survival figures progressively with socioeconomic DEPCAT. However, it should be emphasized that DEPCAT 1, 2, 5, 6 and 7 comprise small numbers and therefore the analyses have been repeated combining DEPCAT to produce zonal groups with similar numbers of cases. These results are summarised in Table 8. Results are also presented diagrammatically in Figure 11. Chi-squared analysis for trend showed a statistically significant difference between groups ($\chi^2 = 6.33$; p=0.011). Patients from lower SES zonal groups have poorer survival rates than the most affluent at 5 years. However the percentage of patients surviving did not increase in a simple progression - in that zone B had the highest survival and zone D the lowest survival. Indeed, if individual zones are compared, B versus C and B versus D are significant (p values respectively p=0.05, p=0.015) (Table 9).

Table 7: survival at 5 years in SES DEPCAT

DEPCAT score	1	2	3	4	5	6	7	Total
Dead at 5 years	12	17	23	40	25	5	5	127
	23.1%	20.7%	18.3%	29.4%	32.9%	38.5%	29.4%	25.3%
Alive at 5 years	40	65	103	96	51	8	12	375
	76.9%	79.2%	81.7%	70.5%	67.1%	61.5%	70.6%	74.7%
Total	52	82	126	136	76	13	17	502

Figure 10: percentage of dead patient at 5 years in DEPCAT, $p = 0.026$

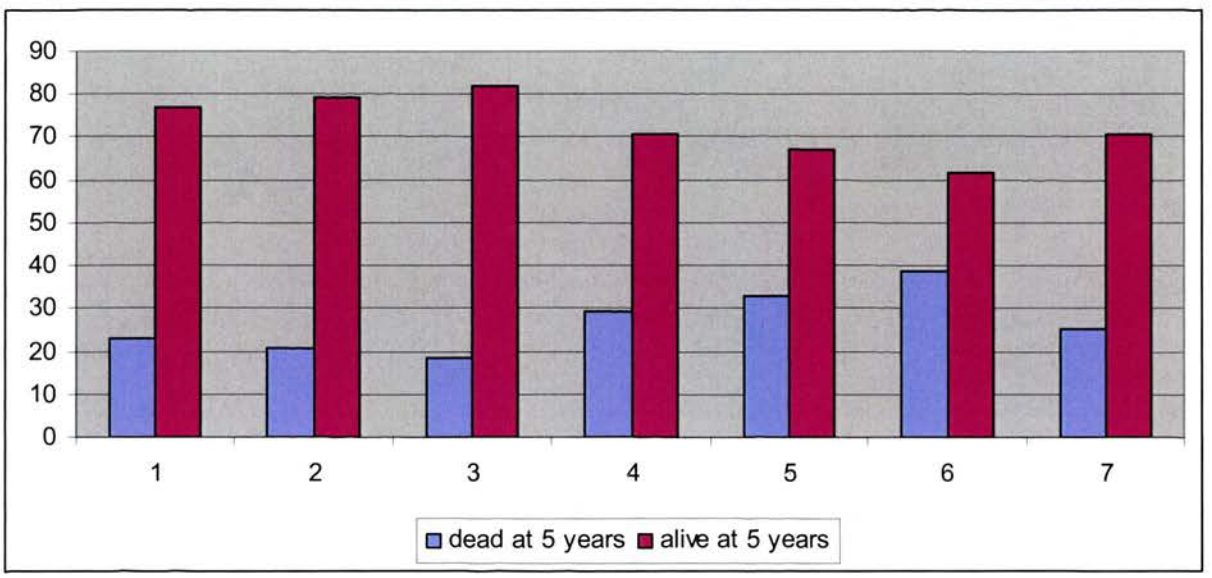


Table 8: survival at 5 years in SES zones, $p = 0.011$

Zones	A	B	C	D	TOTAL
Dead at 5 years	29 21.6%	23 18.3%	40 29.4%	35 33%	127 25.3%
Alive at 5 years	105 78.3%	103 81.7%	96 70.6%	71 67%	375 74.7%
Total	134	126	136	106	502

Figure 11: SES zones and survival at 5 years, $p = 0.011$

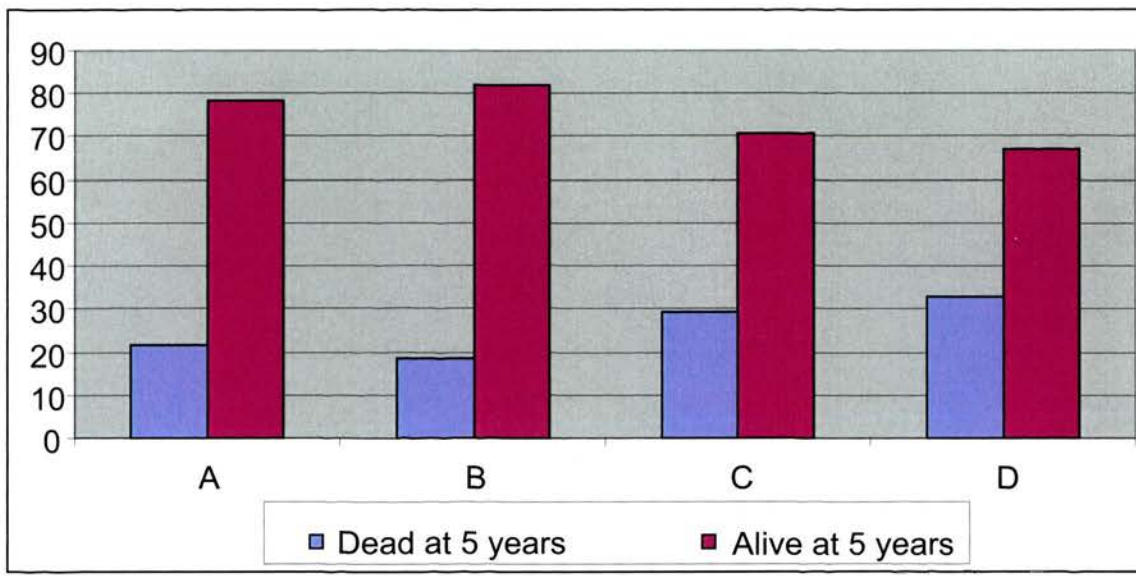


Table 9: *p* values of zones compared separately at 5 years survival (NS: not significant) chi 2 (vertical comparisons) and p values (horizontal comparisons).

	A	B	C	D
A		NS	NS	NS
B	0.25		0.041	0.012
C	0.55	0.66		NS
D	0.093	0.65	0.31	

B – alive or dead at 10 years

Of the total 502 patients, 72 cases were recruited between 1991 and 1993 so that in 2001 when the analyses were performed they had not completed a 10 year follow-up period. This leaves a database of 430 patients in whom outcome at 10 years was known. The number of patients dead at 10 years was 164 (38.1%). The survival figures at 10 years subdivided according to socioeconomic status are summarised in Table 10 and shown diagrammatically in Figure 12. Since the DEPCAT are graded progressively according to SES it was appropriate to apply χ^2 analysis for trend to the data. This produced a χ^2 value of 1.77 and a p value of 0.18. The difference therefore did not reach significance. As with 5 year survival, the analyses have been repeated combining zones to produce groups with similar numbers of cases. These results are summarised in Table 11. Results are also presented diagrammatically in Figure 13. Chi-squared analysis for trend showed that the difference between zonal groups did not reach statistical significance (χ^2=3.938, p=0.0608). However, there was a progressive increase in mortality with increasing social deprivation. Individual group comparisons showed no significant differences (Table 12). Indeed, if individual zones are compared, A versus B, A versus C, A versus D, B versus C and B versus D, and C versus D are not significant (p values respectively p=0.99, p=0.95, p=0.12, p=0.43, p=0.12 and p=0.51).

Table 10: survival for 10 years in different SES DEPCAT

DEPCAT	1	2	3	4	5	6	7	TOTAL
Dead at	17	21	36	46	36	4	4	164
10 yrs	36.1%	32.3%	33.9%	40%	49.3%	40%	28.6%	38.1%
Survived	30	44	70	69	37	6	10	266
at 10 yrs	63.9	67.8%	66%	60%	49.7%	60%	71.4%	61.9%
Total	47	65	106	115	73	10	14	430

Figure 12: survival and dead at 10 years in SES DEPCAT, $p = 0.18$

Table 11: survival for 10 years in different SES zones

ZONES	A	B	C	D
Dead at 10 years	38 33.9%	36 33.9%	46 40.0%	44 45.3%
Alive at 10 years	74 66.1%	70 66.1%	69 60%	53 54.7%
TOTAL	112	106	115	97

Figure 13: survival for 10 years in different SES zones, $p = 0.06$

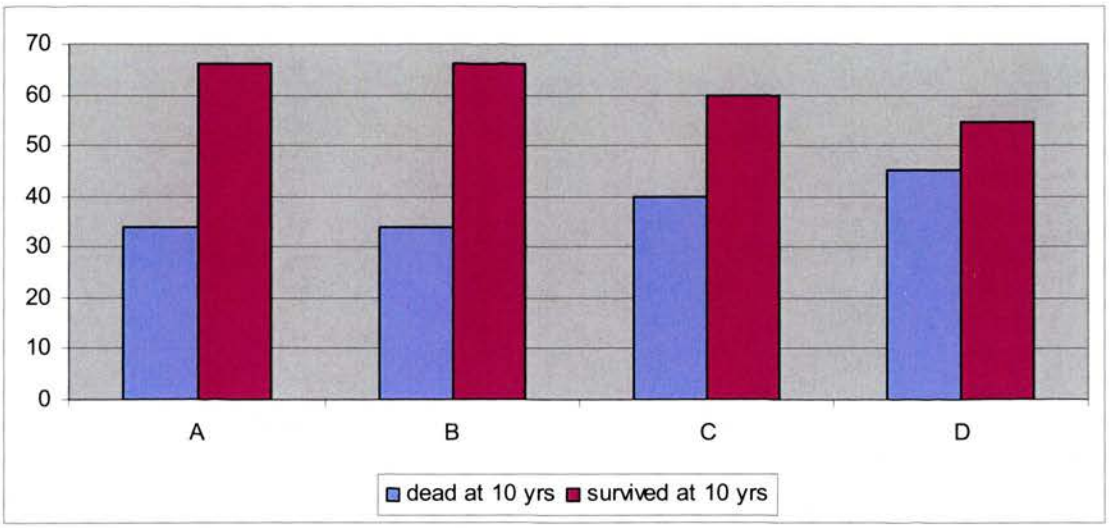


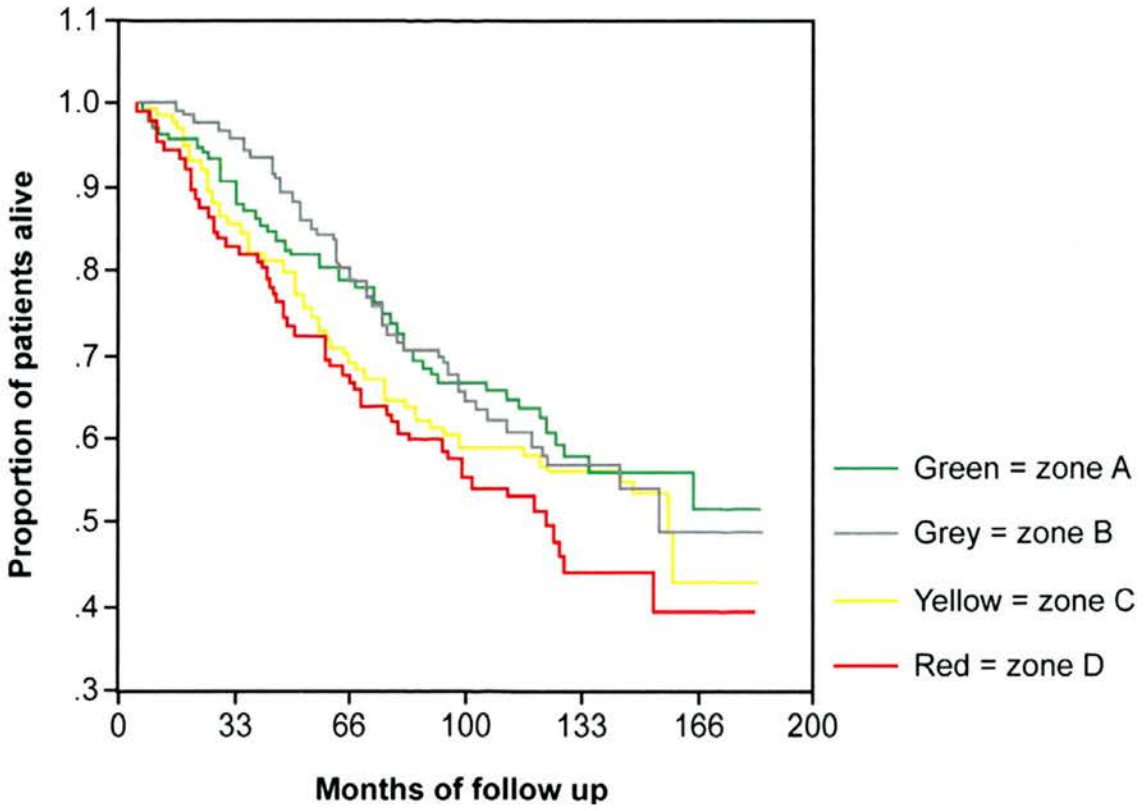
Table 12: *p* values of new zones compared separately at 10 years survival, chi square (vertical comparisons) and p values (horizontal comparisons).

	A	B	C	D
A		0.99	0.95	0.12
B	2.75		0.43	0.12
C	0.0036	0.622		0.51
D	2.39	2.29	0.419	

C - Kaplan-Meier plots

The numbers in socioeconomic DEPCAT 1, 2, 5, 6 and 7 are not sufficiently large to perform meaningful analyses by Kaplan-Meier plot. Therefore these analyses have been restricted to zonal groups. The Kaplan-Meier plot for total patient group overall survival, subdivided according to zones, is illustrated in Figure 14. It can be seen that there was a progressive decrease in survival rate as socioeconomic status decreased. The differences between the curves were statistically significant ($p<0.02$).

Figure 14: Socioeconomic status for total patient group and survival in zones



3.3.3 Recurrence

A - disease-free or recurrent at 5 years

The number of patients recurring at 5 years was 129 (25.7%). The cases subdivided according to socioeconomic status are summarised in Table 13 and shown diagrammatically in Figure 15. The percentage of women recurring at 5 years varied between the DEPCAT groups being lowest in DEPCAT 2 (18.3%) and highest in DEPCAT 5 (32.9%). Since the groups are graded progressively according to SES, chi-squared analysis for trend was applied to the data. This produced a χ^2 value of 2.090 and a p value of 0.1483. It should be noted that despite a lack of significance, there was a trend for recurrence rates to increase with decreasing affluence. However, it should be emphasized that DEPCAT 1, 2, 5, 6 and 7 comprise small numbers and therefore the analyses have been repeated combining zones to produce groups with similar numbers of cases. These results are summarised in Table 14 and also presented diagrammatically in Figure 16. Chi-squared analysis for trend did not reach statistical significance ($\chi^2 = 3.139$; $p = 0.0764$). However, the percentage of patients recurring did tend to increase with increasing social deprivation; zone D had the highest recurrence and zone A the lowest recurrence. Individual zones are compared versus each other (Table 15).

Table 13: recurrence rate up to 5 years in SES DEPCAT

DEPCAT score	1	2	3	4	5	6	7	TOTAL
Recurrence at 5 years	12 23%	15 18.3%	34 27%	35 25.7%	25 33%	4 30.8%	4 23.5%	129 25.7%
No recurrence at 5 years	40 77%	67 81.7%	92 73%	101 74%	51 67%	9 69%	13 76.4%	373 74.3%
Total	52	82	126	136	76	13	17	502

Figure 15: recurrence rate at 5 years in SES DEPCAT, $p = 0.1483$

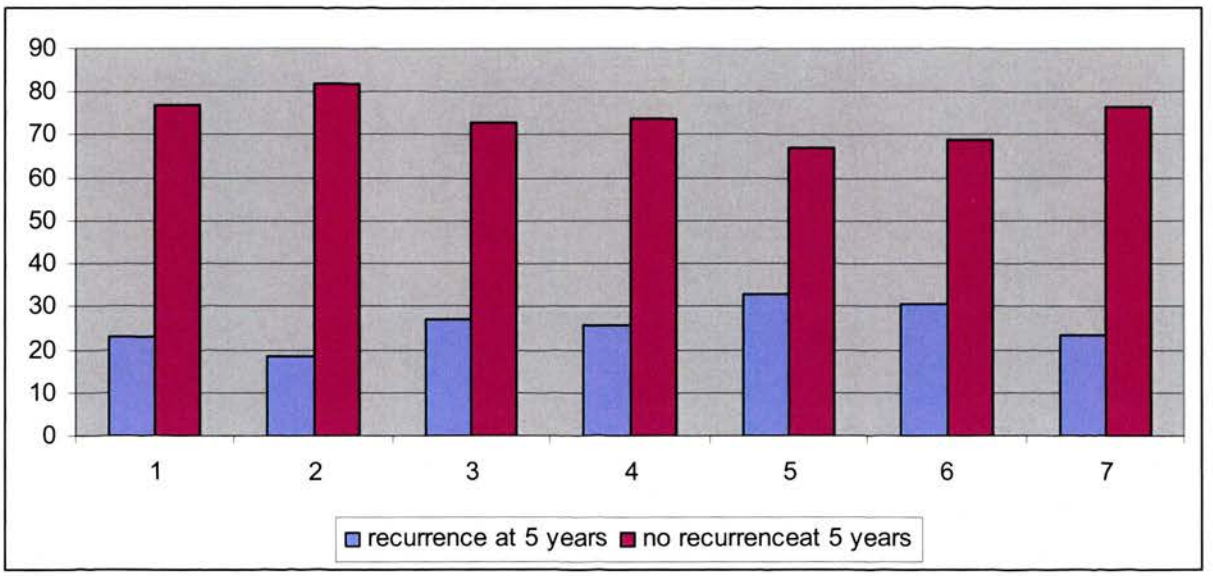


Table 14: recurrence rate up to 5 years in SES zonal groups

ZONES	A	B	C	D	TOTAL
Recurrence at 5 years	27 20%	34 27%	35 25.7%	33 31%	129 25.7%
No recurrence at 5 years	107 80%	92 73%	101 74.2%	73 68.8%	373 74.3%
TOTAL	134	126	136	106	502

Figure 16: recurrence rate up to 5 years in SES zonal groups, $p = 0.0764$

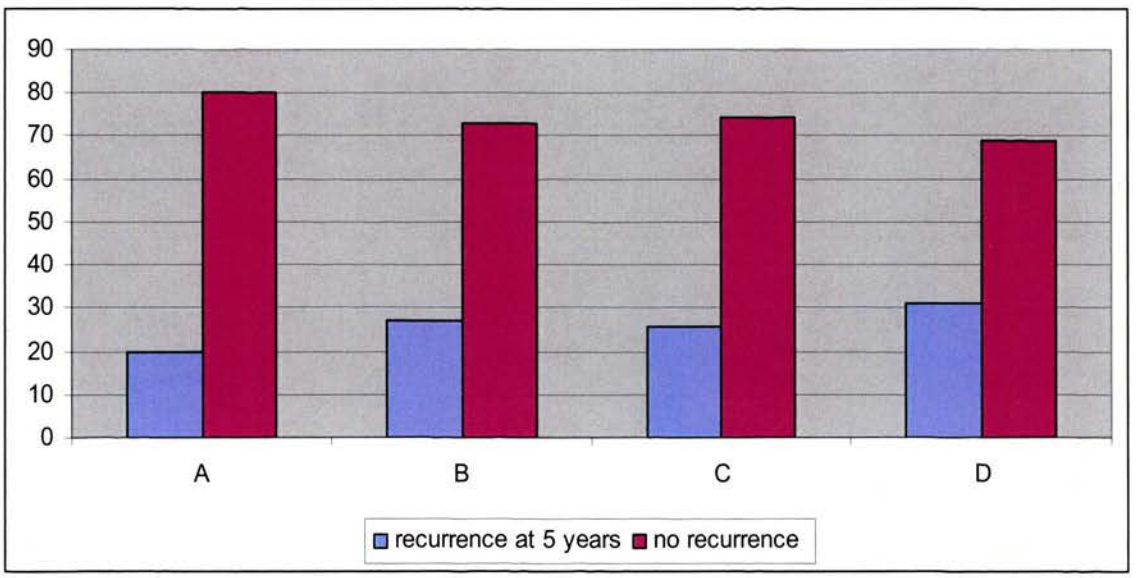


Table 15: *p* values of new zones at 5 years recurrence, chi square (vertical comparisons) and p values (horizontal comparisons)

	A	B	**C**	**D**
A		0.042	0.066	0.0085
B	4.111		0.092	0.58
C	3.380	0.0079		
D	6.931	0.301	0.612	

B – disease-free or recurrent at 10 years

Of the total 502 patients, 72 cases were recruited between 1991 and 1993 so that in 2001 when the analyses were performed they had not completed a 10 year follow-up period. This leaves a database of 430 patients in whom outcome at 10 years was known. The number of patients who recurred at 10 years was 204 (47.4%). The recurrence figures at 10 years subdivided according to socioeconomic status are summarised in Table 16 and shown diagrammatically in Figure 17. The percentage of women with recurrence at 10 years varied between the groups being highest in DEPCAT 5 (56.1%) and lowest in DEPCAT 2 (40%). Since the groups are graded progressively according to SES, chi-squared analysis for trend was applied to the data. This produced a χ^2 value of 3.7 and a p value of 0.053. The difference therefore did not reach significance although there was a trend for increasing recurrence in less socially affluent DEPCAT groups. DEPCAT 1, 2, 5, 6 and 7 comprise small numbers and therefore the analyses have been repeated combining zones to produce groups with similar numbers of cases. These results are summarised in Table 17. Results are also presented diagrammatically in Figure 18. Chi-squared analysis for trend showed that the difference between zonal groups was statistical significant (χ^2=4.6, p=0.03) and there was a progressive increase in recurrence with increasing social deprivation. Individual group comparisons versus A, B, C and D showed no significant differences (Table 18).

Table 16: recurrence rate up to 10 years in SES DEPCAT scores

DEPCAT	1	2	3	4	5	6	7	Total
Recurrence at 10 years	19 40.4%	26 40%	49 46.2%	57 49.5%	41 56.1%	5 50%	7 50%	204 47.4%
No recurrence at 10 years	28 59.6%	39 60%	57 43.8%	58 50.5%	32 45.9%	5 50%	7 50%	226 52.6%
Total	47	65	106	115	73	10	14	430

Figure 17: recurrence at 10 years in SES DEPCAT, $p = 0.053$

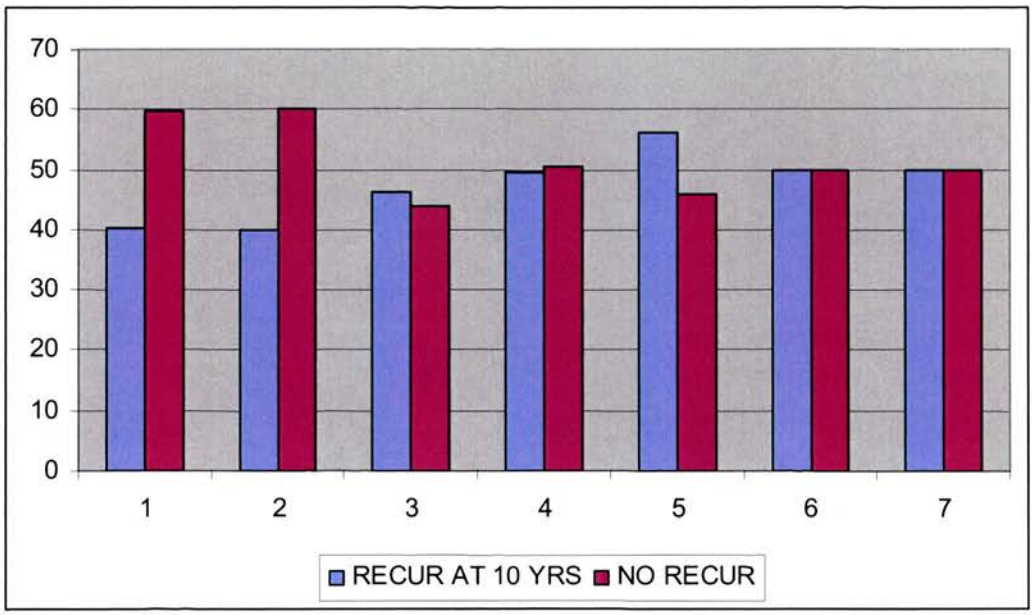


Table 17: recurrence at 10 years in SES zonal groups

zones	A	B	C	D	TOTAL
Recurrence at 10 years	45 40.1%	49 46.2%	57 49.5%	53 54.6%	204 47.4%
No recurrence at 10 years	67 59.9%	57 53.8%	58 50.5%	44 45.4%	226 52.6%
total	112	106	115	97	430

Figure 18: recurrence and disease-free at 10 years in zones, $p = 0.03$

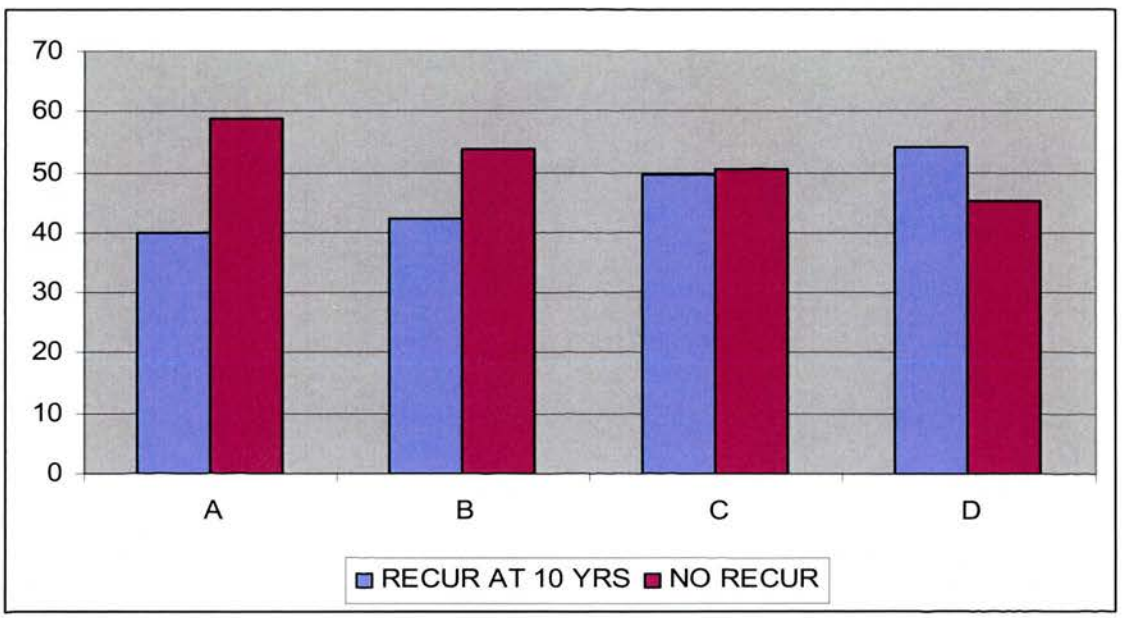


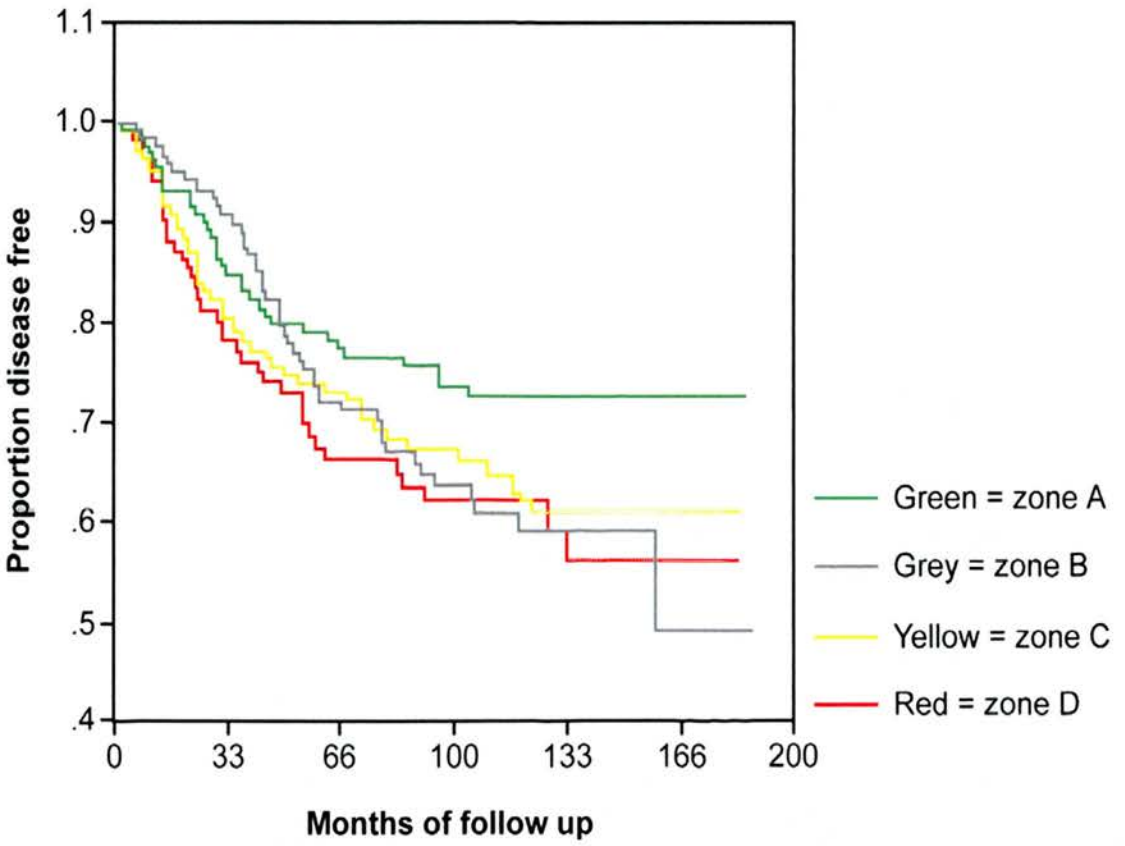
Table 18: *p* values of zones versus 10 years recurrence, chi square (vertical comparisons) and p values (horizontal comparisons) (NS not significant)

	A	B	C	D
A	.	NS	NS	NS
B	0.58		NS	NS
C	0.18	0.13.		NS
D	1.31	1.11	0.36	

C - Kaplan-Meier plots

Because of small number in some DEPCAT categories, Kaplan-Meier analyses have been restricted to zonal groups. The plot for overall recurrence, subdivided according to zones, is illustrated in Figure 19. Whilst the differences between the curves were not statistically significant (p=0.277), it was notable that the most affluent zone appeared to have the best disease-free outcome.

Figure 19: Socioeconomic status and overall recurrence in zones



3.3.4 Correlation of Socioeconomic Status with Established Prognostic Factors

Lymph nodes

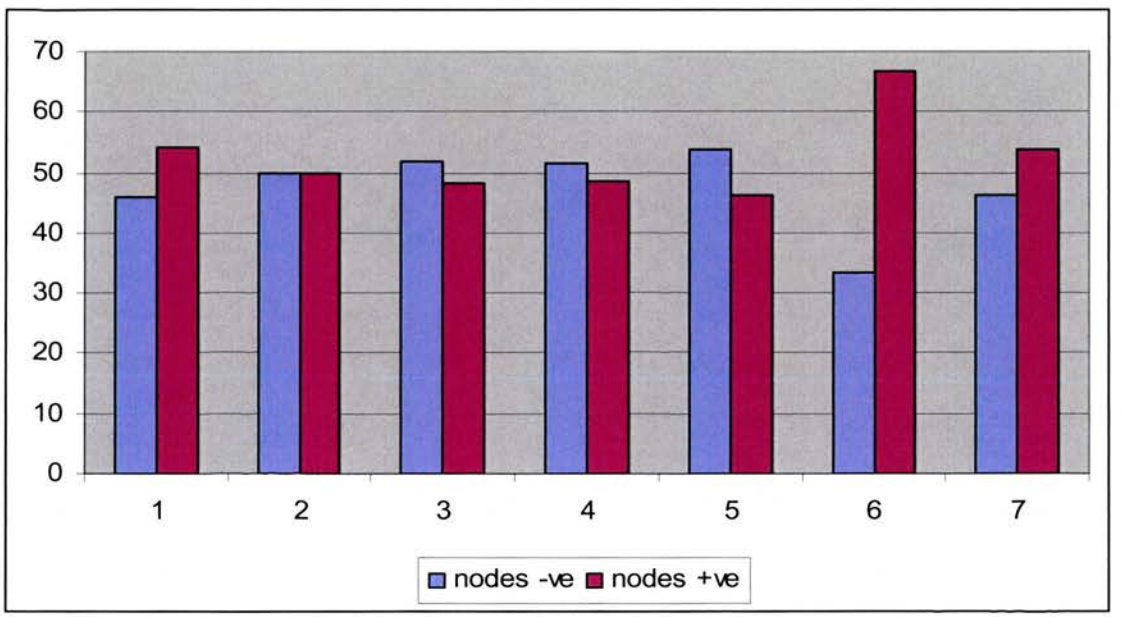
Lymph node status was available in 448 cases. Fifty-four patients did not have their axillary node assessed due to the fact that they were very old and not fit for surgery - their tumours were strongly ER positive and they were treated only with hormonal therapy. Of these patients, 222 (49.5%) were lymph node positive. The incidence of lymph node positivity in each of the socioeconomic zones is presented in Table 19.

Within the SES group of patients without axillary assessment, there were patients in each DEPCAT score but the lowest (7.7%) was in DEPCAT 6, and the highest (23.5%) in DEPCAT 7 (although this is based on only 1 and 4 cases for each DEPCAT respectively). The distribution of lymph node involvement is shown diagrammatically in Figure 20. The % positivity varied between 46.2% (DEPCAT 5) and 66.4% (DEPCAT 6) in different socioeconomic groups. However there was not a statistically significant trend between positivity and socioeconomic DEPCAT (χ^2 for trend 0.02, p=0.881).

Table 19: SES DEPCAT and nodes status

DEPCAT score	1	2	3	4	5	6	7	TOTAL
Node -ve	22 45.8%	37 50%	59 51.7%	63 51.6%	35 53.8%	4 33.4%	6 46.1%	226 50.5&
Node +ve	26 54.2%	37 50%	55 48.3%	59 48.4%	30 46.2%	8 66.6%	7 53.9%	222 49.5%
Total	**48**	**74**	**114**	**122**	**65**	**12**	**13**	**448**

Figure 20: SES DEPCAT and nodes status, *p* value is 0.88



A similar analysis was performed for zonal groups and the data are presented in Table 20 and Figure 21. The % positivity was similar in each group and there was not a statistically significant trend between LN positivity and zonal groups (χ^2 trend 0.077, p=0.78).

The difference between the p values in the groups (A, B, C and D) where comparison is shown in summary between all groups versus each other (Table 21).

Table 20: SES new zones and node status

zone	A	B	C	D	TOTAL
Node -ve	59 48.3%	59 51.7%	63 51.7%	45 50%	226 50.5%
Node +ve	63 51.7%	55 48.3%	59 48.3%	45 50%	222 49.5%

Figure 21: chi squared value, p = 0.78

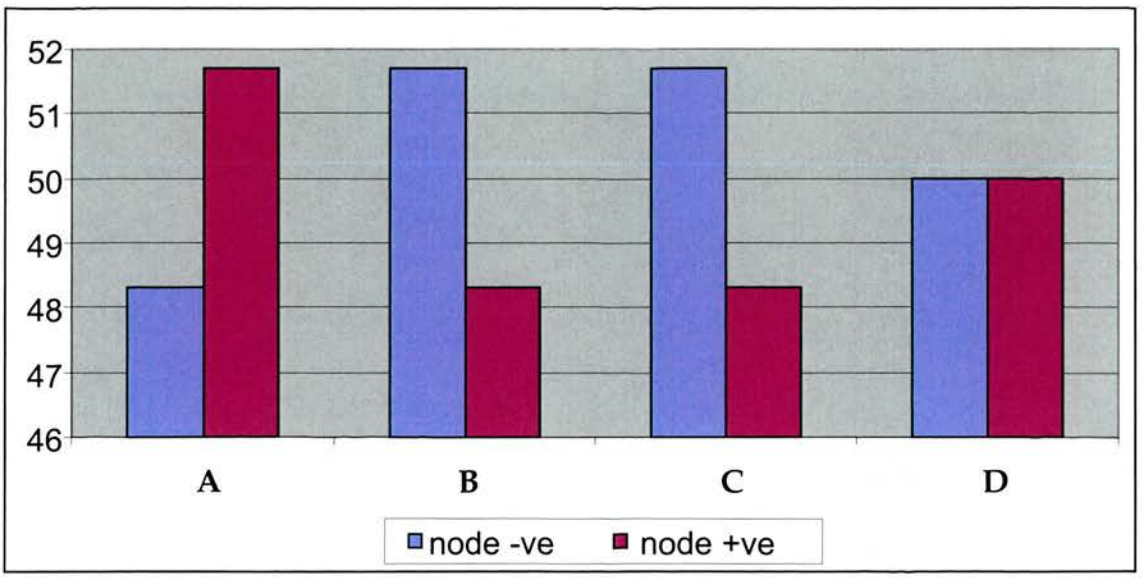


Table 21: *p* values of zones versus lymph nodes status, chi square (vertical comparisons) and p values (horizontal comparisons)

	A	B	C	D
A	.	0.69	0.70	0.92
B	0.152		0.98	0.91
C	0.146	0.0003.		0.92
D	0.0094	0.0116	0.00941	

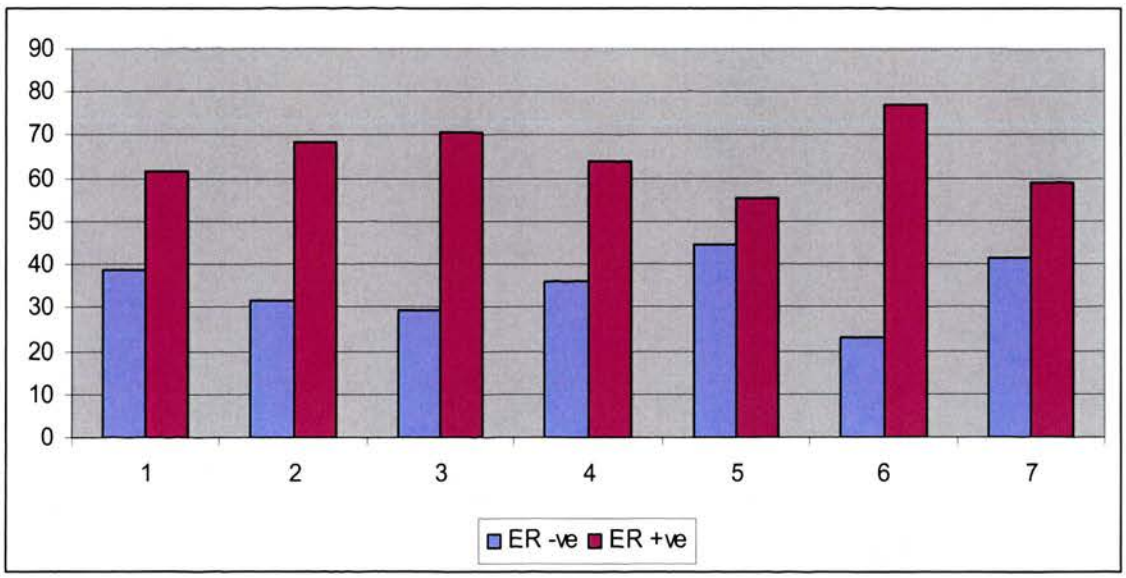
Oestrogen receptor

Oestrogen receptor status was available in all cases, 326 patients (64.9%) were ER positive. The incidence of positivity in each of the socioeconomic DEPCAT is presented in Table 22 and shown diagrammatically in Figure 22. The % positivity varied between 55.3 (DEPCAT 5) and 76.9% (DEPCAT 6) in different socioeconomic groups. However there was not a statistically significant difference between positivity and socioeconomic DEPCAT (χ^2 for trend 6.745, p=0.3367).

Table 22: SES DEPCAT and ER status

DEPCAT score	1	2	3	4	5	6	7	TOTAL
ER -ve	20 38.5%	26 31.7%	37 29.4%	49 36%	34 44.7%	3 23.1%	7 41.2%	176 35.1%
ER +ve	32 61.5%	56 68.3%	89 70.6%	87 64%	42 55.3%	10 76.9%	10 58.8%	326 64.9%
Total	52	82	126	136	76	13	17	502

Figure 22: SES DEPCAT and ER status, P value is 0.33

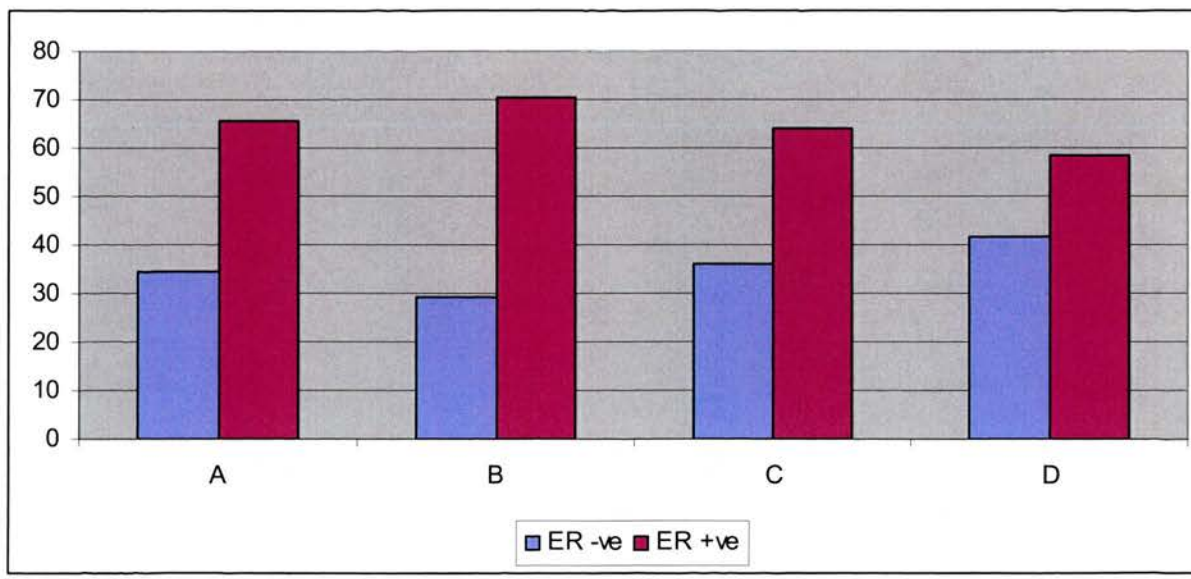


A similar analysis was performed for zonal groups and the data are presented in Table 23 and Figure 23. The % negativity varied from 29.4% to 41.5% (B and D respectively) and there was not a statistically significant trend between ER positivity on zonal groups (χ^2 trend 3.819, p=0.1728).

Table 23: SES zonal group and ER status

ZONE	A	B	C	D	TOTAL
ER -VE	46 34.3%	37 29.4%	49 36%	44 41.5%	176 35.1%
ER +VE	88 65.7%	89 70.6%	87 64%	62 58.5%	326 64.9%
Total	134	126	136	106	502

Figure 23: SES zonal group and ER status, P value is 0.1728



The difference between the groups (A, B, C and D) versus each other is shown for comparison in Table 24.

Table 24: *p* values of zones versus ER status, chi square (vertical comparisons) and p values (horizontal comparisons)

	A	B	C	D
A	·	0.27	0.86	0.31
B	1.203		0.35	0.072
C	0.0272	0.860.		0.46
D	1.014	3.221	0.542	

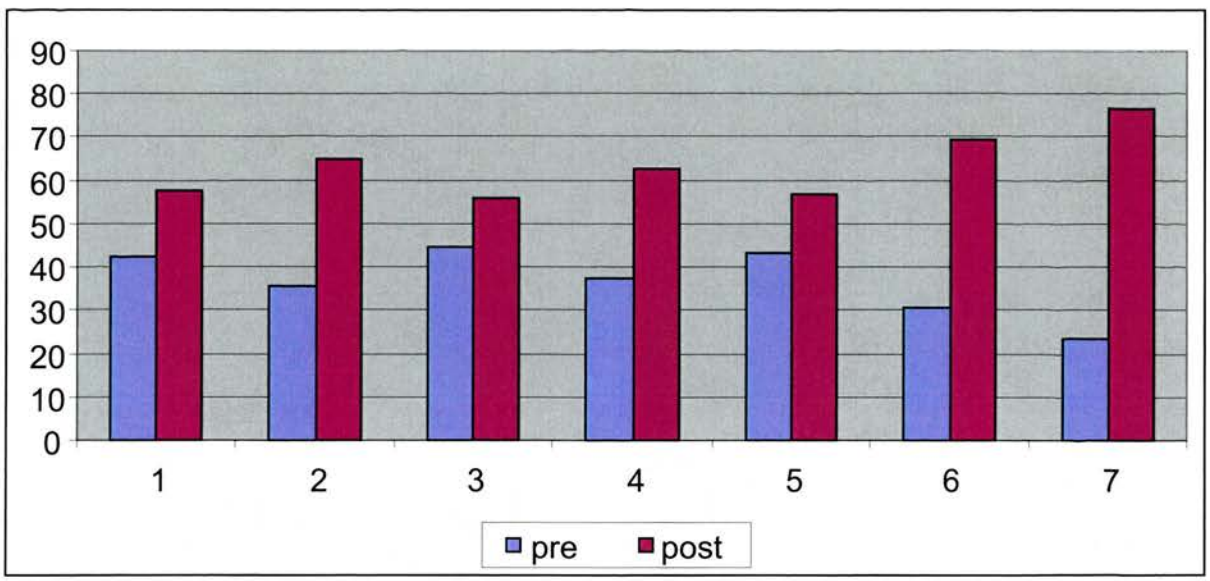
Menopausal status

Menopausal status was available in all cases. There were 199 premenopausal and 303 postmenopausal patients. The menopausal status in each of the socioeconomic DEPCAT is presented in Table 25 and shown diagrammatically in Figure 24. The % premenopausal varied between 43.4% (DEPCAT 5) and 30.8% (DEPCAT 6) in different socioeconomic groups. However there was not a statistically significant difference between menopausal status and socioeconomic DEPCAT; χ^2 for trend 1.124, p =0.4899.

Table 25: SES DEPCAT and menopausal status

DEPCAT score	1	2	3	4	5	6	7	TOTAL
PRE	22 42.30%	29 35.40%	56 44.40%	51 37.50%	33 43.40%	4 30.80%	4 23.50%	199 39.60%
POST	30 57.70%	53 64.60%	70 55.60%	85 62.50%	43 56.60%	9 69.20%	13 76.50%	303 60.40%
Total	52	82	126	136	76	13	17	502

Figure 24: SES DEPCAT and menopausal status, p = 0.4899

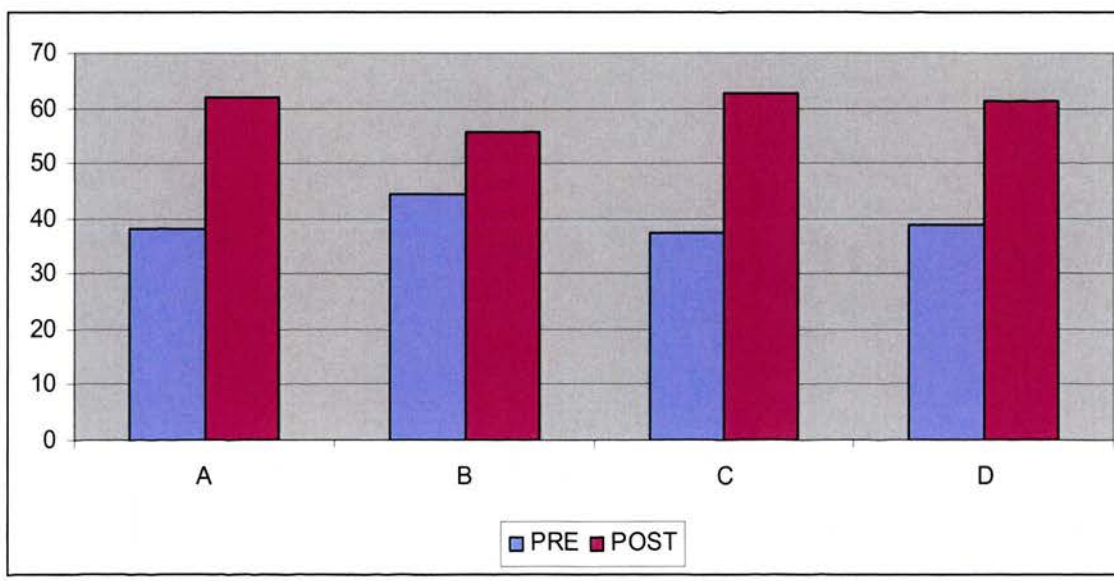


A similar analysis was performed for zonal groups and the data are presented in Table 26 and Figure 25. The % premenopausal varied from 37.5% to 44.4% (C and B respectively) and there was not a statistically significant trend between menopausal status on zonal groups; χ^2 for trend 1.657, p= 0.8135 (Table 26).

Table 26: SES zonal groups and menopausal status

Zones	A	B	C	D	TOTAL
PRE	51 38.1%	56 44.4%	51 37.5%	41 38.7%	199 39.60%
POST	83 61.9%	70 55.6%	85 62.5%	65 61.3%	303 60.40%
Total	134	126	136	106	502

Figure 25: SES zonal groups and menopausal status, p = 0.8135



The difference between p values of the groups (A, B, C and D) is shown for comparison in Table 27.

Table 27: *p* values of zonal groups versus menopausal status, chi square (vertical comparisons) and p values (horizontal comparisons)

	A	B	C	D
A	.	0.357	0.924	0.921
B	0.845		0.275	0.451
C	0.00899	1.189.		0.950
D	0.0096	0.567	0.00292	

T stage

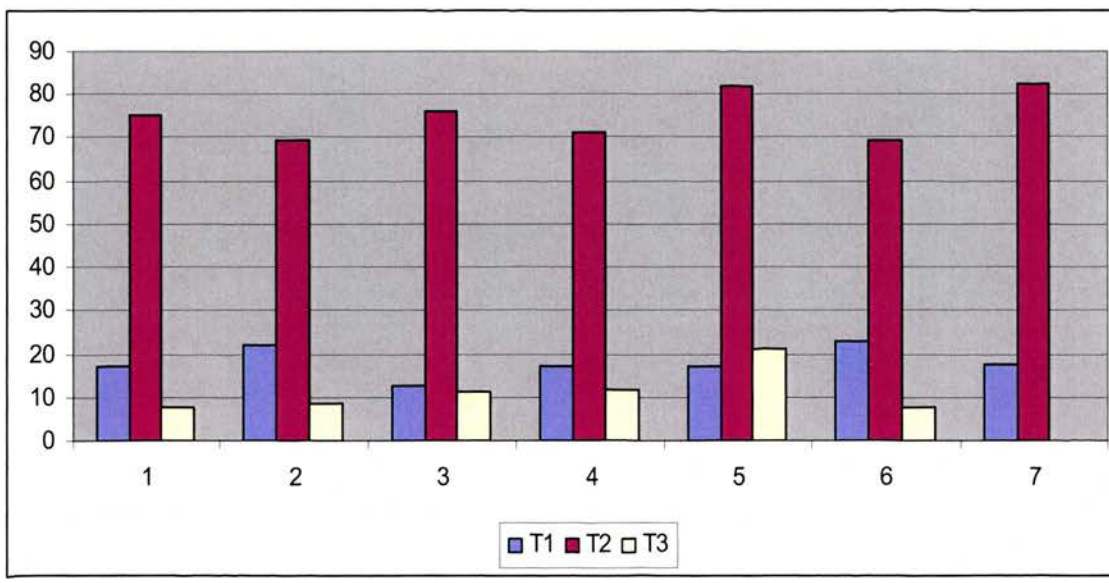
The staging used is the TNM classification, UICC International Union Against Cancer; the number of patients with DCIS was 13 and they were excluded from the study. Because the number of patients in T3 and T4 were low they were included together as T3/4. There were 85 patients in T1, 359 in T2 and 58 patients in T3/4 (54 in T3 and 4 in 4).

Each of the socioeconomic DEPCAT is presented in Table 28 and shown diagrammatically in Figure 26.

Table 28: SES DEPCAT and T stage tumours

DEPCAT score	1	2	3	4	5	6	7	TOTAL
T1	9 17.3%	18 22%	16 12.7%	23 16.9%	13 17.1%	3 23.1%	3 17.6%	85 16.9%
T2	39 75%	57 69.5%	96 76.2%	97 71.3%	47 61.8%	9 69.2%	14 82.4%	359 71.5%
T3/4	4 7.7%	7 8.5%	14 11.1%	16 11.8%	16 21.1%	1 7.7%	0 0%	58 11.6%
Total	**52**	**82**	**126**	**136**	**76**	**13**	**17**	**502**

Figure 26: SES DEPCAT scores and tumour staging, $p = 0.296$

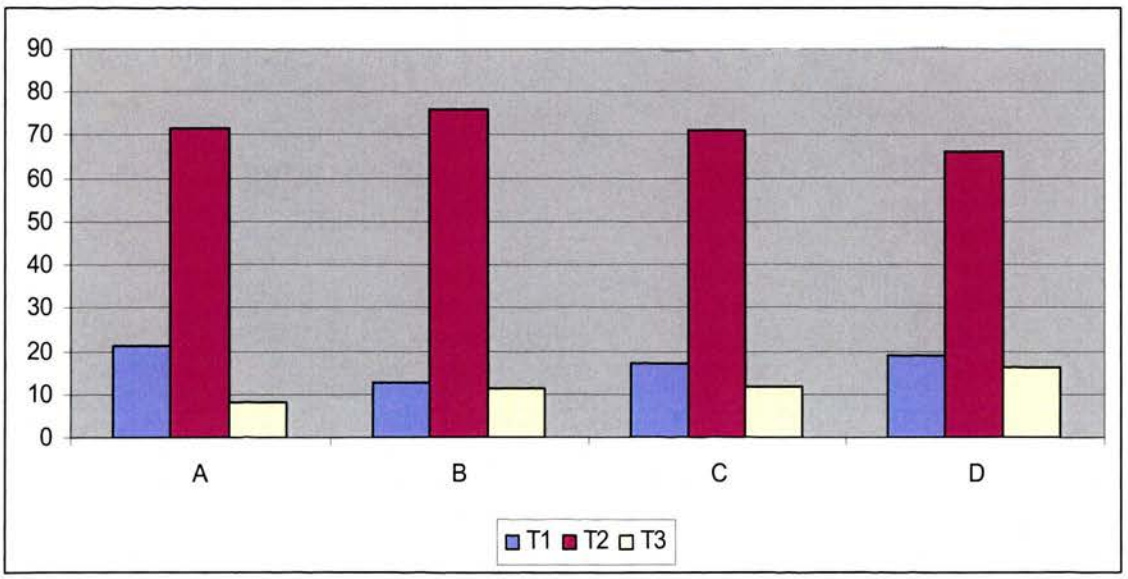


The % of T stage varied between 23.1%% (DEPCAT 6) and 12.7% (DEPCAT 3) for T1 in different socioeconomic DEPCAT, 82.4 % (DEPCAT 7) and 61.8% (DEPCAT 5) for T2 and 21.1 % (DEPCAT 5), and 0 (DEPCAT 7) for T3. However there was not a statistically significant difference between T stage and socioeconomic and DEPCAT scores (χ^2 for trend 14.00, $p = 0.296$). Similar analysis was performed for zonal groups and again it was not significant statistically (χ^2 value is 6.214, p=0.400). These data are presented in Table 29 and Figure 27.

Table 29: SES zonal group and T staging tumour size

ZONE	A	B	C	D	TOTAL
T1	27 20.1%	16 12.7%	23 16.9%	19 17.9%	85 16.9%
T2	96 71.6%	96 76.2%	97 71.3%	70 66%	359 71.5%
T3/4	11 8.2%	14 11.1%	16 11.8%	17 16%	58 11.6%
Total	**134**	**126**	**136**	**106**	**502**

Figure 27: SES zonal groups and tumour staging, $p = 0.400$



The difference between the p values between the groups (A, B, C and D) is shown for comparison (Table 30).

Table 30: *p* values of zones versus T stage, chi square (vertical comparisons) and *p* values (horizontal comparisons)

	A	B	C	D
A	.	0.099	0.289	0.159
B	2.711		0.573	0.966
C	1.121	0.3161.		0.650
D	1.976	0.00181	0.2052	

3.3.5 Correlation of established prognostic factors with outcome

Lymph node involvement is a very well documented prognostic factor for survival; more involved lymph nodes, worse will be the survival.

Lymph node status

Of the 502 patients, 448 cases had lymph node status documented 222 (49.5%) were lymph node positive.

5 year survival

Of the 222 lymph positive cases, 68 (30.6%) had died by 5 years. The number of deaths in the lymph node negatives was 34 of 226 (15.0%), an incidence half that of the lymph node positive group. By chi-squared analysis the difference in death rate between LN-ve and LN+ve patients was highly significant (χ^2 value is 14.60, p=0.0001).

	Alive	**Dead**
LN-ve	192	34 (15.0%)
LN+ve	154	68 (30.6%)

10 year survival

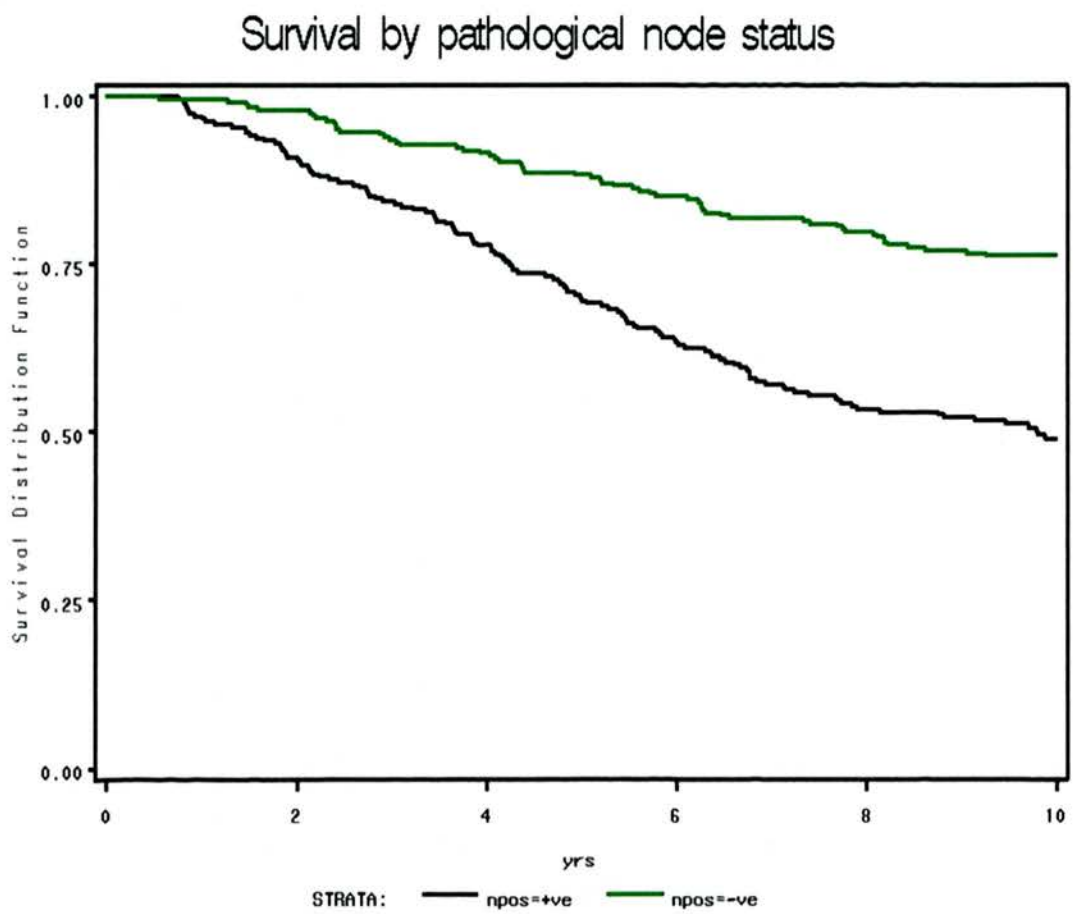
Of the total 502 patients, 72 cases were recruited between 1991 and 1993 so that in 2001 when the analyses were performed they had not completed a 10 year follow-up period. This leaves a database of 430 patients in whom outcome at 10 years was known. Of these patients, 384 cases had lymph node status documented. Of these, 193 (48.9%) were lymph node positive. Of the lymph positive cases, 89 (46.1%) had died by 10 years. The number of deaths in the lymph node negatives was 48 of 191 (25.1%). By chi-squared analysis the difference in death rate between LN-ve and LN+ve patients was highly significant (χ^2=17.52, p=0.0001).

	Alive	**Dead**
LN-ve	143	48 (25.1%)
LN+ve	104	89 (46.1%)
(χ^2=7.52, p=0.0001)		

Kaplan-Meier

The Kaplan-Meier plot for overall survival, subdivided according to lymph node involvement, is illustrated in Figure 28. It can be seen that there was a progressive fall in survival rate between negative and positive lymph node involvement. The differences between the curves were statistically significant ($p< 0.0001$).

Figure 28



Oestrogen receptor

All of the 502 patients had their ER status documented (176 (35.1%) were ER negative).

5 year survival

Of the 176 ER negative cases, 68 (38.6%) had died by 5 years. The number of deaths in the ER positive was 55 of 271 (16.8%), an incidence almost double that of the ER negative group. By chi-squared analysis the difference in death rate between ER-ve and ER+ve patients was highly significant (χ^2=28.1, p=0.001).

	Alive	**Dead**
ER-ve	108	68 (38.6%)
ER+ve	271	55 (16.8%)
(χ^2=28.1, p=0.001)		

10 year survival

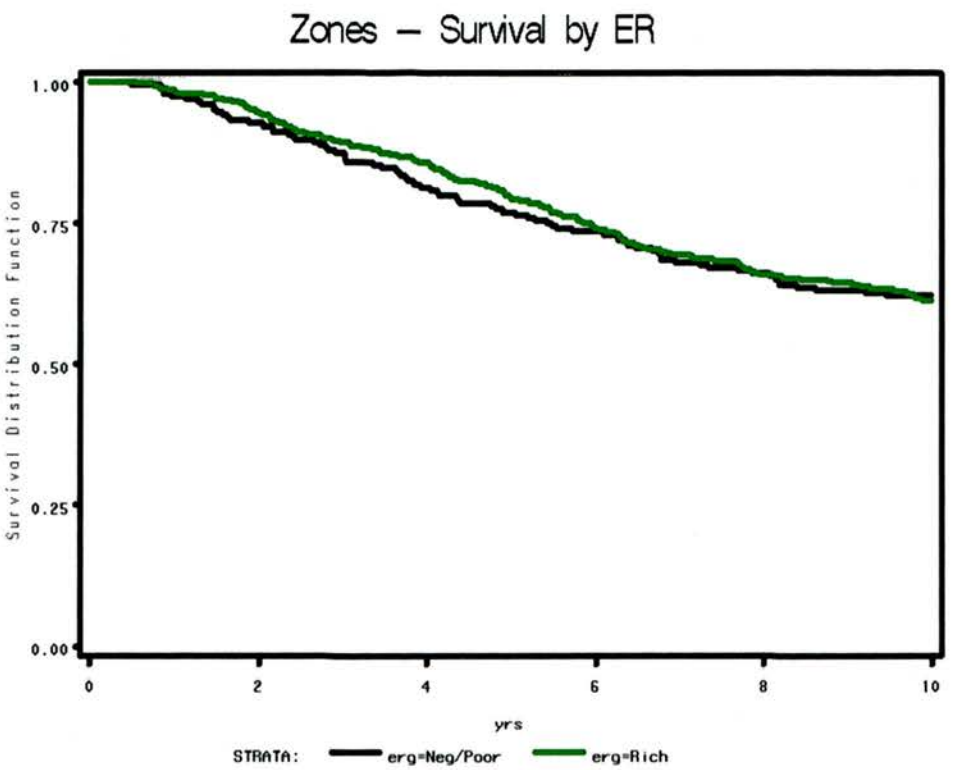
As mentioned above, out of the total 502 patients, 72 cases were recruited between 1991 and 1993 so that in 2001 when the analyses were performed they had not completed a 10 year follow-up period. This leaves a database of 430 patients in whom outcome at 10 years was known. Of these, 157 (35.1%) were ER negative. Of the ER negative cases, 69 of 157 (43.9%) had died by 10 years. The number of deaths in ER positive was 95 of 273 (34.8%). By chi-squared analysis the difference in death rate between ER-ve and ER+ve patients was not significant (χ^2=3.16, p=0.076).

	Alive	**Dead**
ER-ve	88	69 (43.9%)
ER+ve	178	95 (34.8%)
(χ^2=3.16, p=0.076)		

Kaplan-Meier

The Kaplan-Meier plot for overall survival, subdivided according to ER status, is illustrated in Figure 29. It can be seen that there is no change in survival rate with ER status. The differences between the curves were statistically not significant (p<0.211).

Figure 29



T stage

All of the 502 patients had their T stage documented (85 (16.9%) were T1, 359 (71.5%) T2, and 58 (11.6%) were T3/4).

5 year survival

Of the 85 T1 cases, 22 (25.8%) had died by 5 years. The number of deaths in the T2 was 83 of 359 (23.2%), and 18 (31%) of 58 in T3/4. By chi-squared analysis the difference in death rate between T1, T2 and T3/4 patients was not significant (χ^2=0.26, p=0.609).

	Alive	**Dead**
T1	63	22 (25.8%)
T2	276	83 (23.2%)
T3/4	40	18 (31.0%)
(χ^2=0.26, p=0.609)		

10 year survival

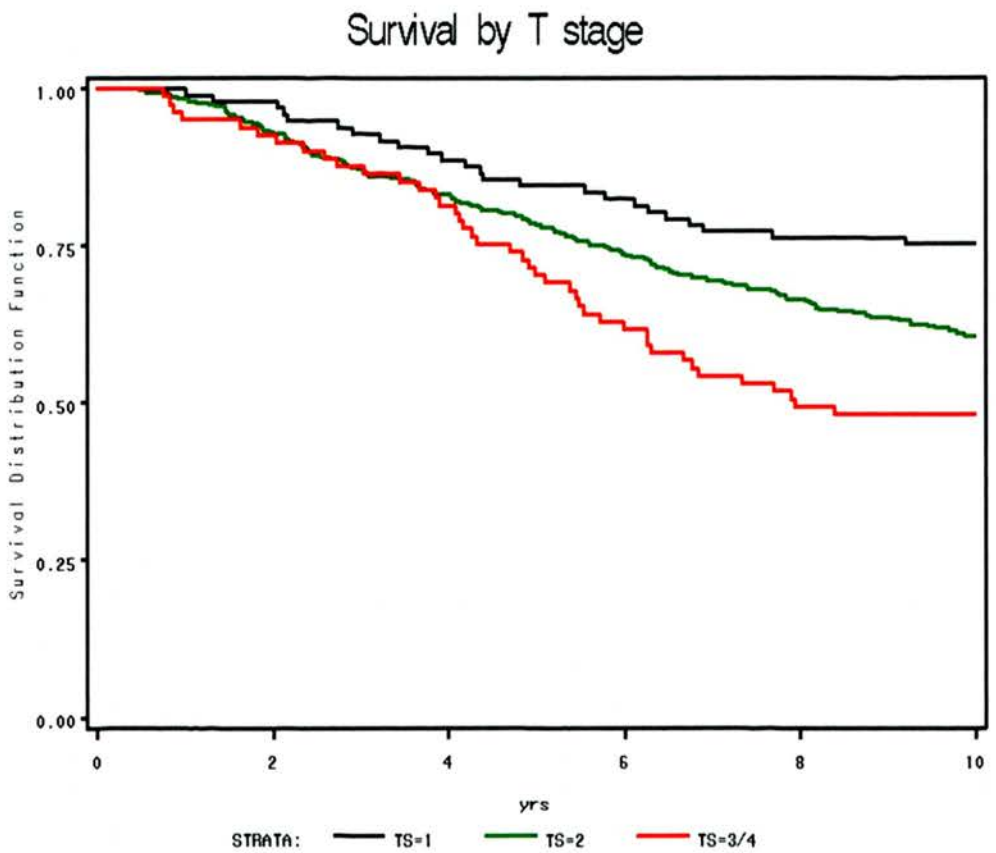
Of the total 502 patients, 72 cases were recruited between 1991 and 1993 so that in 2001 when the analyses were performed they had not completed a 10 year follow-up period. This leaves a database of 430 patients in whom outcome at 10 years was known. Of these, 18 (25%) were T1. Of the T2 cases, 121 of 306 (39.5%) and 25 cases from T3/4 of 52 cases had died by 10 years. By chi-squared analysis the difference in death rate between T1, T2 and T3/4 patients was highly significant (χ^2=7.37, p=0.007).

	Alive	**Dead**
T1	54	18 (25.0%)
T2	185	121 (39.5%)
T3/4	27	25 (48.1%)
(χ^2=7.37, p=0.007)		

Kaplan-Meier

The Kaplan-Meier plot for overall survival, subdivided according to T stage, shows a progressive decrease in survival rate as the T stage increases. The differences between the curves were statistically significant (p<0.0061) (Figure 30).

Figure 30: survival by T stage, p = 0.0061



Menopausal status

The menopausal status was classified in all women as either premenopausal (regular menstrual periods) or postmenopausal (at least 3 years beyond their last menstrual period). All of the 502 patients had their menopausal status documented (199 (39.6%) were premenopausal status and 303 (60.4%) postmenopausal).

5 year survival

Of the 199 premenopausal cases, 48 (24.1%) had died by 5 years. The number of deaths in the postmenopausal was 75 (24.7%) of 303, an incidence almost the same in each group. By chi-squared analysis the difference in death rate between menopausal status patients was insignificant (χ^2=0.0003, p=0.956).

	Alive	**Dead**
Premenopausal	151	48 (24.1%)
Postmenopausal	228	75 (24.7%)
(χ^2=0.0003, p=0.956)		

10 year survival

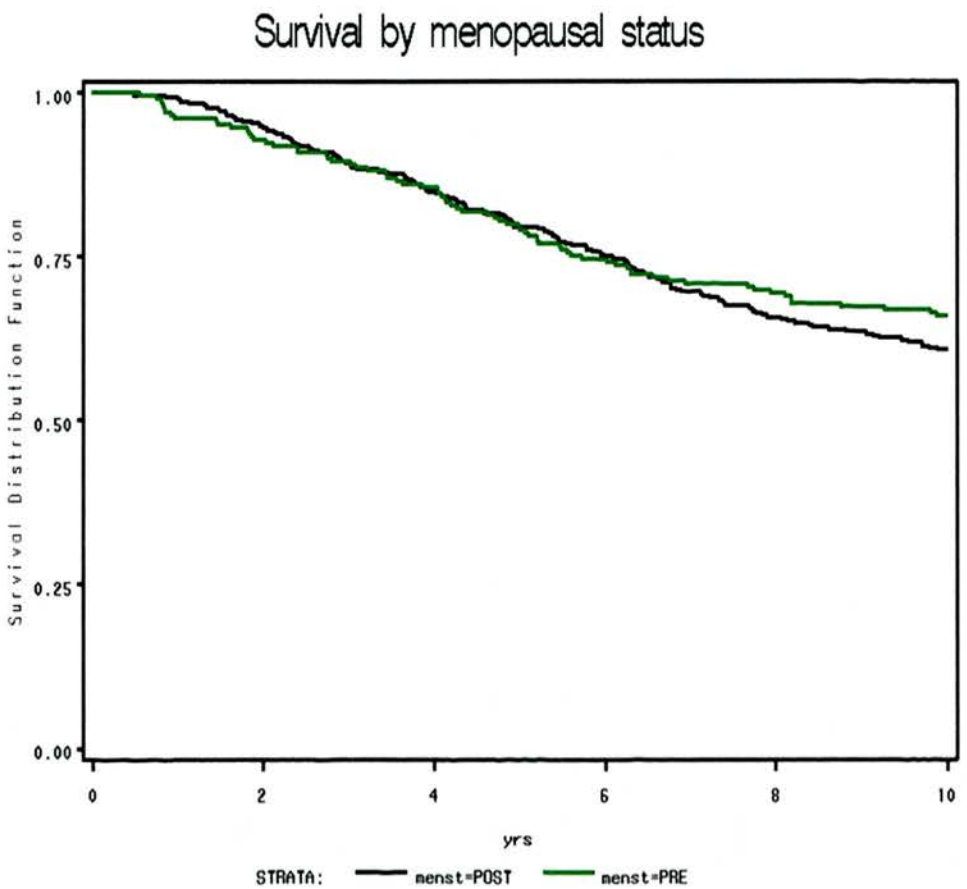
Of the total 502 patients, 72 cases were recruited between 1991 and 1993 so that in 2001 when the analyses were performed they had not completed a 10 year follow-up period. This leaves a database of 430 patients in whom outcome at 10 years was known. Of these, 60 (30.1%) were premenopausal. Of the postmenopausal cases, 104 of 303 (34.6%) had died by 10 years. By chi-squared analysis the difference in death rate between menopausal status patients was insignificant (χ^2=1.07 p=0.30).

	Alive	**Dead**
Premenopausal	112	60 (30.1%)
Postmenopausal	154	104 (34.6%)
(χ^2=1.07, p=0.30)		

Kaplan-Meier

The Kaplan-Meier plot for overall survival, subdivided according to menopausal status is illustrated in Figure 31. It can be seen that there is no change in survival rate with menopausal status. The differences between the curves were statistically not significant (p<0.1834).

Figure 31: survival by menopausal status, p< 0.1834



3.3.6 Recurrence

Lymph node status

As was mentioned above in Survival, not all patients had their axillary dissection surgery. As a result of this, out of the 502 patients, 448 cases had lymph node documented (222 (49.5%) were lymph node positive).

5 year recurrence

The number of recurrences in the lymph node negatives was 50 (22.1%) of 226, and of the 222 lymph positive 90 (40.5%) had recurred cases by 5 years. The incidence of recurrence almost doubled in lymph node positive group. By chi-squared analysis the difference in recurrence rate between LN-ve and LN+ve patients was highly significant (χ^2=16.83, p=0.0001).

	DF	**REC**
LN-ve	176	50 (22.1%)
LN+ve	132	90 (40.5%)
(χ^2=16.83, p=0. 0001)		

10 years recurrence

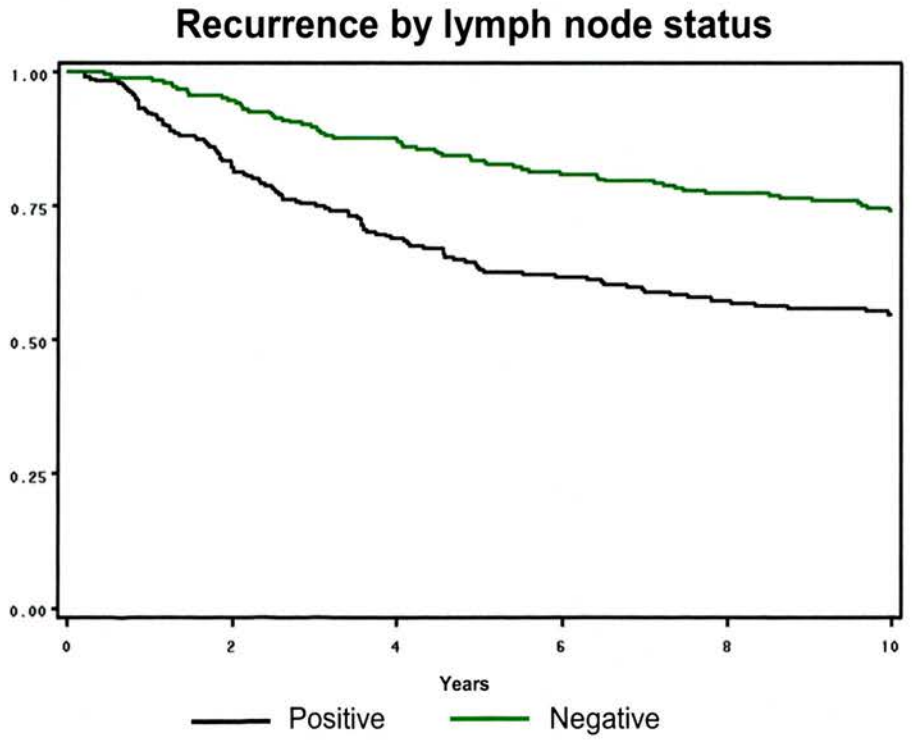
Of the 193 lymph positive cases, 106 (54.9%) had recurred by 10 years. The number of recurrences in the lymph node negative group was of 70 of 191 cases (36.6%). By chi-squared analysis the difference in recurrence rate between LN-ve and LN+ve patients was highly significant (χ^2=12.18, p=0.0005).

	DF	**REC**
LN-ve	121	70 (36.6%)
LN+ve	87	106 (54.9%)
(χ^2=12.18, p=0. 0005)		

Kaplan-Meier

The Kaplan-Meier plot for recurrence, subdivided according to lymph node involvement, is illustrated in Figure 32. It can be seen that there was a progressive increase in recurrence rate as lymph node involvement increases. The differences between the curves were statistically significant (p<0.0001).

Figure 32: Kaplan-Meier p of <0.0001



Oestrogen receptor

All 502 patients had their ER status documented. 176 (35.1%) were ER negative and 326 (64.9%) were ER positive.

5 year recurrence

The number of recurrences in the ER negatives was 76 (43.1%) of 176, and of the 326 ER positive 86 (26.3%) had recurred cases by 5 years. The incidence of recurrence is higher in ER negative group. By chi-squared analysis the difference in recurrence rate between ER-ve and ER+ve patients was highly significant (χ^2=14.00, p=0. 0002).

	DF	**REC**
ER-ve	100	76(43.1%)
ER+ve	240	86 (26.3%)
(χ^2=14.00, p=0. 0002)		

10 years recurrence

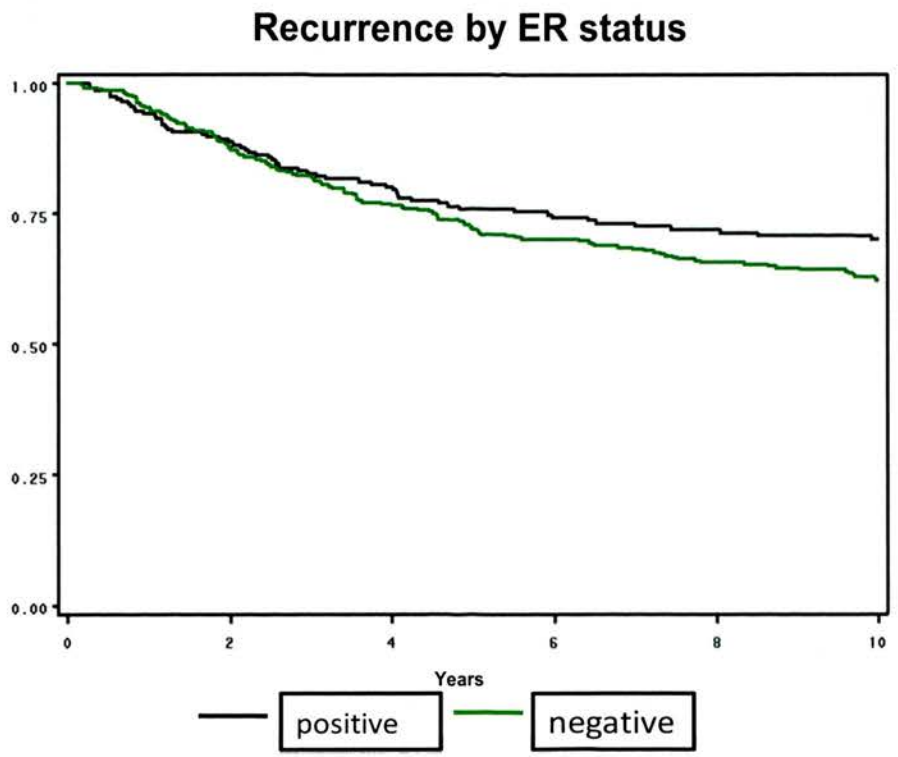
Of the 273 ER positive cases, 129 (47.2%) had recurred by 10 years. The number of recurrences in the ER negative group was 75 of 157 cases (47.7%). By chi-squared analysis the difference in recurrence rate between ER-ve and ER+ve patients is not significant (χ^2=1.066, p= 0.99).

	DF	**REC**
ER-ve	82	75 (47.7%)
ER+ve	144	129 (47.2%)
(χ^2=, 1.066 p=0.99)		

Kaplan-Meier

The Kaplan-Meier plot for recurrence, subdivided according to ER status, is illustrated in Figure 33. It can be seen that there is change in recurrence rate with ER status. The differences between the curves were statistically significant (p<0.010).

Figure 33: Kaplan-Meier p value of 0.010



T stage

All of the 502 patients had their T stage documented (85 (16.9%) were T1, 359 (71.5%) T2 and 58 (11.6%) were T3/4).

5 year recurrence

129 patients had recurrence at 5 years (25.7%) and 373 were disease free. 24 (28.2%) of 85 developed recurrence in T1 group, 113 (31.4%) had recurrence at 5 years in T2 group, and 25 (43.1%) in T3/4 group of 58 cases. By chi-squared analysis the difference in recurrence rate at 5 years between T1, T2 and T3/4 patients was not significant (χ^2=3.05 p=0.08).

	DF	**REC**
T1	61	24 (28.2%)
T2	246	113 (31.4%)
T3/4	33	25 (43.1%)
(χ^2=3.05, p=0.08)		

10 years recurrence

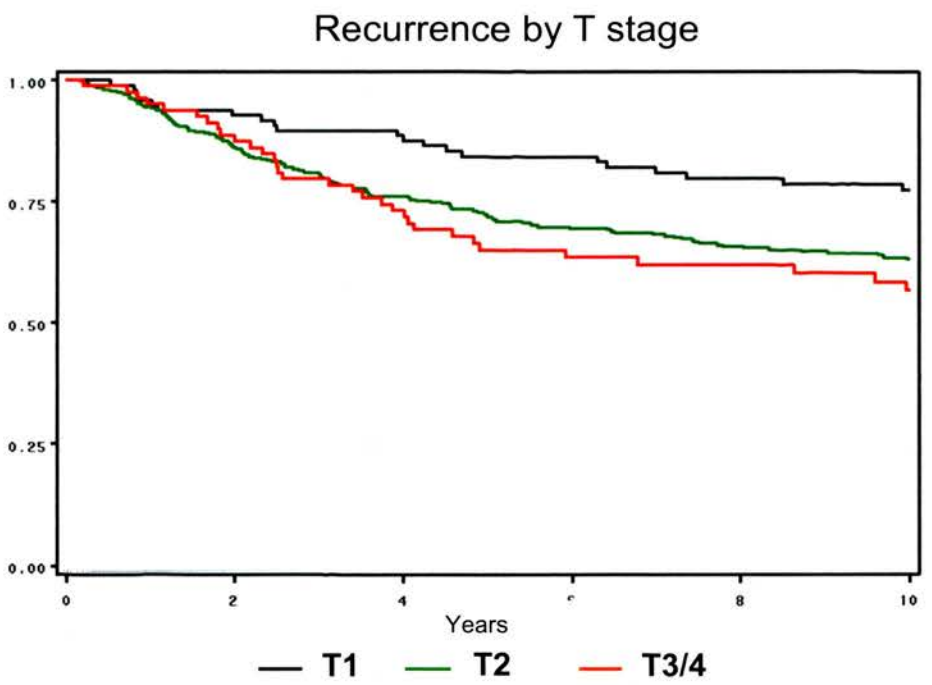
Of the total 502 patients, 72 cases were recruited between 1991 and 1993 so that in 2001 when the analyses were performed they had not completed a 10 year follow-up period. This leaves a database of 430 patients in whom outcome at 10 years was known. Of these, 26 (36.1%) had recurrence at 10 years of 72 cases in T1, 149 (48.6%) of 306 cases in T2 and 29 (55.7%) of 52 cases in T3/4 had recurrence at 10 years. By chi-squared analysis the difference in recurrence rate between T1, T2 and T3/4 patients was highly significant (χ^2=5.08, p=0.024).

	DF	**REC**
T1	46	26 (36.1%)
T2	157	149 (48.6%)
T3/4	23	29 (55.7%)
(χ^2=5.08, p=0.024)		

Kaplan-Meier

The Kaplan-Meier plot for recurrence, subdivided according to T stage (Figure 34) shows a progressive increase in recurrence rate as the T stage increases. The differences between the curves were statistically significant (p<0.0238).

Figure 34: Kaplan-Meier p value of 0.0238



Menopausal status

The menopausal status was classified in all women as either premenopausal (regular menstrual periods), postmenopausal (at least 3 years beyond their last menstrual period [148]. All of the 502 patients had their menopausal status documented (199 (39.6%) were classified as premenopausal and 303 (60.4%) postmenopausal).

5 year recurrence

Of the 199 premenopausal cases, 69 (34.6%) had recurrence at 5 years. The number of recurrence in the postmenopausal was 93 (30.7%) of 303, an incidence which is almost the same in both groups. By chi-squared analysis the difference in recurrence rate between menopausal status patients was insignificant (χ^2=0.70, p=0.40).

	DF	**REC**
Premenopausal	130	69 (34.6%)
Postmenopausal	210	93 (30.7%)
(χ^2=0.70, p=0.40)		

10 years recurrence

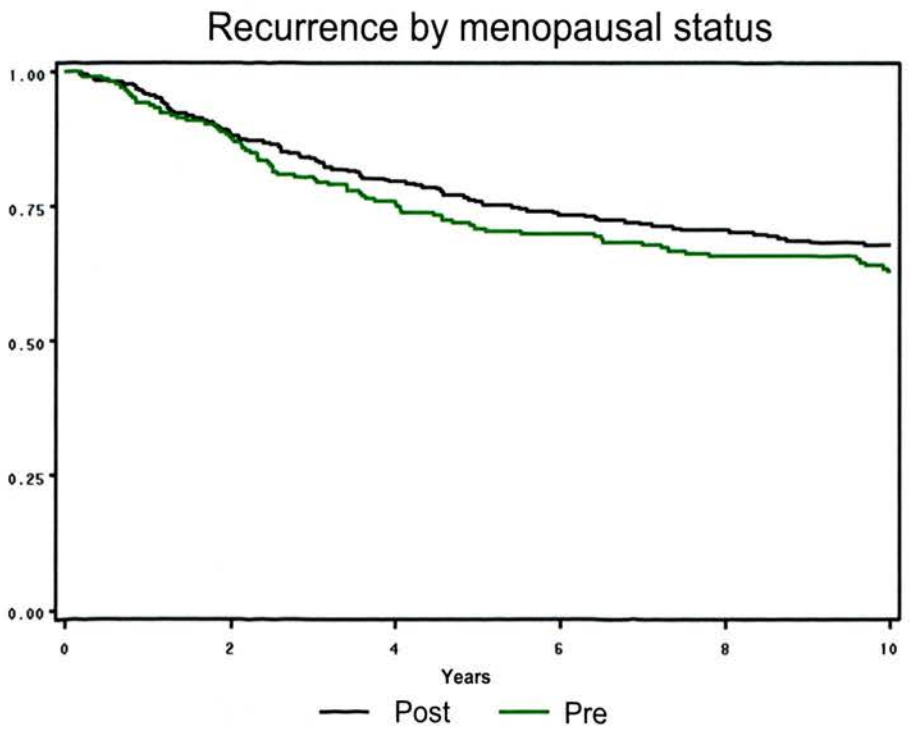
As mentioned earlier with regards to survival at 10 years, not all patients had 10 year follow-up. As a result of this, out of the total 502 patients, 72 cases did not have 10 years follow-up for recurrence. This leaves a database of 430 patients in whom recurrence at 10 years was known. Of these, 82 (47.6%) were premenopausal. Of the postmenopausal cases, 122 of 258 (48.2%) had recurrence by 10 years. By chi-squared analysis the difference in death rate between menopausal status patients was insignificant (χ^2=20.1, p=0.93).

	DF	**REC**
Premenopausal	90	82 (47.6%)
Postmenopausal	136	122 (47.2%)
(χ^2=0.01, p=0.93)		

Kaplan-Meier

The Kaplan-Meier plot for recurrence, subdivided according to menopausal status is illustrated in Figure 35. It can be seen that there is no change in survival rate with menopausal status. The differences between the curves were statistically not significant (p<0.18).

Figure 35: Kaplan-Meier p of 0.18



3.3.7 Multivariate analysis (Proportional hazards analysis)

Multivariate analyses were performed including the following possible prognostic variables Year treated, Age, Menopausal status, T stage , ER(status), Clinical size, lymph nodes status (Number of +ve nodes), and Zone (socio-economic status).

SURVIVAL

Only 441 patients out of 502 have information on all these variables for survival and can be included in the analysis.

Prognostic variables independently significant for survival are shown in Table 31; variables not significant, ie socio-economic status, were not included.

Table 31: Survivals and variable with significant p values and hazards

Variable	P	Hazard
Number of +ve nodes	<0.0001	Increasing
Size	<0.0001	Increasing
Year treated	0.0004	Increasing
ER	0.0474	Decreasing

Recurrence

Only 441 patients out of 502 were included in the analysis, the same 8 variables as above were considered as possible prognostic variables for recurrence, again socio-economic status was not significant.

Table 32: Recurrence and variable with significant p values and hazards

Variable	P	Hazard
Number of +ve nodes	<0.0001	Increasing
Size	0.0009	Increasing
Age	0.0046	Decreasing
Year treated	0.0225	Increasing

3.4 Discussion

The outcome of breast cancer is variable even in patients presenting with same stage of disease. Many factors may account for this and parameters such as tumour size, lymph node involvement, ER receptors status and menopausal status have been implicated. Despite this it is clear that there are other variables which can be influential. These include the SES and background of the patient. Although SES has been extensively studied with regard to risk of breast cancer factors (and there is a consensus that women from affluent backgrounds are at increased risk) investigations focusing on the outcome of established breast cancer are less frequent. Furthermore, not all studies have detected significant relationship, and those that had usually have found that social deprivation is associated with worse outcome (the reverse of the association with risk).

There are several advantages in looking at the potential relationship between SES and breast cancer outcome in women living in the southeast of Scotland. Thus, most of the women diagnosed with breast cancer are referred to the Edinburgh Breast Unit. This Unit represents the major referral centre for the southeast of Scotland and sees over 90% of patients from this area. These patients are routinely and rigorously followed up and given standardized treatment according to Unit policy, regardless of the socioeconomic background.

This geographic population of the southeast of Scotland is relatively stable and can be stratified into different socioeconomic groups according to postcode of residence. Carstairs Index has been used in several successful studies in Scotland and worldwide.

The patient population investigated in this study was referred to the Edinburgh Breast Unit between 1985 and 1993 so that when analyses were performed all had a follow-up of at least 8 years. Cases were selected on the basis that tumour material

from the patients had been stored in liquid nitrogen for investigation within the scope of this present study. As a consequence, the series constituted only a minority of the breast cancer cases diagnosed in southeast Scotland. However, there are no reasons to believe that the cases studied were not representative of the overall population and have normal demographic in terms of clinical outcome.

To confirm that this was indeed the case, correlations have been established between prognostic factors and outcome. Thus in the present study population established poor prognosis factors, such as increasing T stage and lymph node involvement, were highly significantly associated with early recurrence and death from breast cancer as reported previously [66, 229].

Similarly, increasing T stage was generally associated with poor outcome being significantly (and inversely) related to overall survival and recurrence (positively) by Kaplan-Meier analysis.

Positive ER status is generally thought to have favourable prognostic factors, although it does appear as significant in some studies. This would be consistent with the findings in the present study in which ER positive tumours were significantly less likely to recur early (Kaplan-Meier at 5 year analysis, but not 10 years); ER status and survival at 5 years was significant at 5 years but was not significant at 10 years and for Kaplan-Meier. In terms of menopausal status, no significant association was found with outcome, recurrence or survival, which is again compatible with published literature.

The major analyses in the study were the correlations between SES and long-term clinical outcome. Associations have been made with death from breast cancer and recurrence of breast cancer. For each of these parameters multiple statistical testing has been performed with regards to time of follow-up (at 5 years, 10 years and over the total follow up period) and category of socioeconomic grouping (DEPCAT and zones).

Whist this has advantages in providing different perspective, it also has the disadvantage in that multiple testing may give rise to spurious significant results and inconsistence. In drawing conclusions, emphasis should be given to consistency of associations and greater reliance attached to Kaplan-Meier (which utilises total follow up data) and zones (which contain greater number of cases).

In term of survival, findings generally indicated that increased social deprivation was associated with adverse outcome. This was evident in the 5 year figures and also Kaplan-Meier analysis of total analysis (the trend was similar at 10 years but did not reach significance, presumably because of the lower number of events). These results would be compatible with other studies, most notably in the west of Scotland.

With regard to recurrence rates, similar trends of poorer outcome for less affluent women were apparent. However, with the exception of recurrence rates for zonal analysis at 10 years, none of these reached statistical significance, despite the increased number of events compared with survival data. It can only be a matter of hypothesis as to why associations are stronger between SES and survival compared with recurrence.

In an effort to determine factors which might have contributed to a poorer outcome of socially deprived women, the relationship between SES and known prognostic factors was also examined.

No significant relationship was found between LN status, T stage status, ER status and menopausal status. It is therefore unlikely that these parameters contributed to the adverse survival data of the socioeconomically deprived. It is important to compare these results with previously published data. Whilst there are reports that socially deprived women present with more advance disease in terms of LN involvement and larger tumours, the literature equally contains publications which show no association.

Menopausal status was not statistically significant between premenopausal and socioeconomic zone. Other studies looked at the relationship between SES and age, which suggest younger women have poorer survival. In younger women (30-64 years), the survival gradient by deprivation category cannot be explained by these prognostic factors [198].

The present study did not show an association between tumour ER status and patients' SES, although several studies (including one in the west of Scotland) have suggested that patients from socially deprived areas are more likely to have ER negative tumours and because of this will have a poorer prognosis [191].

Whilst the lack of correlation between SES and tumour ER, stage and treatment in the present study mean that the latter parameters individually cannot account for the relationship between SES and long-term survival, in multivariate analysis, prognostic variables such as lymph node status, ER status, age and clinical tumour size were the only independently significant for survival and recurrence. It seems likely therefore that these parameters in combination may be able to account for the effects of SES.

CHAPTER 4

GENERAL DISCUSSION

Whilst the investigation in Chapter 2 on the location of the primary tumour within the breast in two groups of patients diagnosed 40 years apart and Chapter 3 on the effects of socioeconomic status on prognostic factors and outcome of patients with breast cancer may appear to be separate, and indeed can stand alone, they have in common (i) the need for a comprehensive and well-validated database of patients presenting with breast cancer and (ii) that the cases of breast cancer are derived from a well-defined and stable population. The cases of breast cancer diagnosed in the southeast of Scotland and/or referred to the Edinburgh Breast Unit fulfil these criteria.

The studies linking social history to either presentation of breast cancers or the impact of social economic status on clinical outcome have made use of data collected on breast cancer in the Edinburgh Breast Unit which covers a vast area of southeast Scotland, and offers good and equal treatment to all patients regardless of their social background. Access to the records and files of homogenous patients relating to breast cancer and its' outcome, and whether the disease has changed in its appearance over time, made these studies possible.

By comparing records from 1957-1959 with those from 1997-1999 it was possible to demonstrate that the location of breast cancer within the breast has changed with time. The most significant difference in the cancers between the cohorts was the decrease in tumour size. Similar changes over time have been previously reported. This is likely to be in large part because of better education, with increasing breast awareness and the introduction of the screening programme in Edinburgh in 1991. The present study has confirmed previously reported findings that the distribution of breast cancer is not even throughout the breast but is higher in the upper outer

quadrant (UOQ). There was an increase in the likelihood of finding a cancer in the lower outer quadrant (LOQ).

Although this has been formally published in only one study in the UK in which incidence of breast cancer in the UOQ rose disproportionately from 38.3% in 1980 to 54.7% in 2001 [138], and is true for countries as diverse as India [125], the West Indies [126] and Italy [127], and irrespective of race from the same country [128], it is interesting to note that the reported incidence of breast cancer in the UOQ appears to rise disproportionately with year of publication [134-136] which would be in keeping with the present observations.

In 1926, 30.9% of breast cancer was reported to be in the UOQ [133], but reports between the years 1947-1967 suggested that the proportion of breast cancer in the UOQ was 43-48%. A study in 1994, reported 60.7% of breast cancers in the UOQ [127].

This change in location is a reflection of other changes over time in the incidence and behaviour of breast cancer. Thus, the overall incidence of breast cancer is rising in Britain [163, 164] and indeed all over the world [15, 230, 231]. Also the staging has changed, more early breast cancer being seen compared with the past. This might be due to the efficiency of the screening mammogram.

The histology of breast cancer has also changed, as has been mentioned in Chapter 2. Ductal carcinoma incidence rates remained essentially constant, while lobular carcinoma rates increased steadily [163, 164].

Even when looking at the laterality of breast cancer incidence, there is change in the laterality. Earlier studies showed that the left breast is more prone to development of cancer than the right breast, in both female and male [124-126, 140, 142, 160, 161]. In a more recent study, the numbers of right-sided and left-sided breast cancer incidence were roughly equal [161] and the present study showed the laterality of

incidence is almost identical (no changes between left and right in breast cancer incidence between the two cohorts).

Although elsewhere breast cancer is rising in women of all socioeconomic status in Scotland and the deprived-affluent gap remains [180], the exact causes behind these observations are not fully defined and, indeed, it is likely that the differential effects may be multifactorial.

There is a long-standing awareness that poverty is associated with general risk of ill-health and outcome from disease. However, some of the reasons underlying the phenomenon include lifestyle factors such as diet, stress, reproductive and child-bearing parity, the use of oral contraceptives, HRT, radiation and environmental factors, but it cannot be excluded that the increased incidence in more affluent populations is due to more efficient diagnosis of the disease.

Although social background, lifestyle and environment have changed markedly in Scotland over the last 40 years, it would appear that there is a consistency with regard to SES and outcome. The present study confirms the poorer survival of patients from low SES areas. This was also noted in earlier published reports.

The major conclusions of this study are that:

i) presentation of breast cancer in terms of location within the breast has changed with time.
ii) despite major changes in lifestyle the outcome of patients from deprived SES is poorer than in more affluent women. The underlying causes for these observations are largely undefined but they could provide clues as to the causes of breast cancer and the changes in detection and natural history of the disease, and also illustrate the potential of analysing data stored in stable databases from major referral centres such as the Edinburgh Breast Unit.

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