Breast Cancer Chemoprevention: Economic and Policy Considerations

Alison Patricia Frater
London School of Hygiene and Tropical Medicine

Abstract

The potential for chemoprevention of breast cancer depends on the benefits being achieved at reasonable cost. This study assesses the economics of chemoprevention of breast cancer with tamoxifen within the context of the International Breast Cancer Intervention Study (IBIS) and published data on outcomes.

Anonymised trial data are used to measure direct resource costs based on the pattern of service delivery in the IBIS clinics. Changes in morbidity are measured as the differences in use of resources for hospital visits, procedures undertaken in hospital, use of prescribed medications and visits to GPs between women in the 2 arms of IBIS. Changes in quality of life are assessed using the SF 36. Information on the personal costs to the women themselves was gained through a postal questionnaire.

A sensitivity analysis assesses the effects on cost effectiveness of alternative assumptions about the duration of the protective effect of tamoxifen (5,10 or 15 years) beyond the treatment period. Other alternative assumptions explored include different models of service delivery, differences in personal costs to the women themselves and in their risk status.

Tamoxifen chemoprophylaxis for breast cancer has a cost of less than £5000 per discounted life year gained for women at high risk for the disease assuming that the protective effect persists for at least 10 years. This result is sensitive to the risk status of the women since the number needed to treat (NNT) would be high for women at low absolute risk of breast cancer. The model of service delivery is also important. No significant differences in morbidity between the groups were found. Hospital visits for benign breast disease or gynaecological symptoms and the use of beta blockers may merit further investigation. There appear to be no effects on quality of life.

Chemoprevention of breast cancer could be delivered through general practice with minimal specialist support. The potential may be limited because of the need to target women at high risk in order to make efficient use of resources for this common condition.

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The economics and policy implications of tamoxifen chemoprophylaxis for breast cancer.

Introduction

This thesis is concerned with the economics and policy implications of use of the drug tamoxifen to prevent breast cancer in women at high risk for the disease. The work has been developed alongside the International Breast Cancer Intervention Study (IBIS) [1]. Results from other chemoprevention studies are also used particularly the NSABP P-1[2].

Economic analysis requires detailed information about the effects of an intervention on survival and general health as well as information about changes in resource use arising directly from the intervention and for the target population. In this case it will include the resource consequences of delivering a service for tamoxifen chemoprophylaxis, possible changes in health care resources due to side effects of the intervention and resource implications for the women themselves both in terms of changes in personal costs incurred or in quality of life. In order to inform the policy implications an understanding of acceptability and likely uptake among the target population is also needed as well as comparative information on alternative means of reducing mortality and morbidity from breast cancer.

The information needed on the efficacy of the intervention has been based on target assumptions developed within IBIS and from the findings of NSABP P-1. Detailed information on use of hospital services and medications has been taken from the data collected from women enrolled in IBIS. The information has been used to develop methodologies for understanding the resource consequences of changes in morbidity for women taking prophylactic tamoxifen.

Other specific studies used to inform the economic analysis include detailed measurements of the resources used in delivering the intervention based on the models adopted within IBIS centres and a study of the resource consequences for the women themselves. This latter study was carried out by means of a questionnaire sent

to women enrolled in IBIS. Information was collected on the costs of IBIS to the women themselves, on quality of life and on use of primary care services.

It was not possible to use unblinded information from IBIS since the trial has not yet completed. It was however possible to obtain data sets separated into 2 anonymised groups. This enabled understanding of the significance of any differences in resource use between the 2 groups. Conclusions have been drawn about the key factors affecting the cost effectiveness of tamoxifen prophylaxis and its likely range given currently available information. Once the trial has been concluded the methodology and approach developed here can be used to conclude the economic analysis. Information to inform policy has been developed from a detailed review of the published literature on the aetiology of breast cancer and the impact of current therapeutic interventions. A discussion of the potential for primary prevention with dietary intervention is also included.

IBIS is continuing to recruit towards its target of 7,000 women with the aim of providing crucial information on the impact of tamoxifen on both incidence and mortality from breast cancer. As a consequence it may also be possible to address questions concerning the characteristics of the women most likely to benefit from prophylactic tamoxifen and the nature of tumours which do arise. Such information would contribute to more detailed understanding of the cost effectiveness of the intervention for women at different levels of risk of breast cancer. As part of the continuing data collection further information will be available on the use of medications and hospital services by women in IBIS. This will contribute to the analysis of resource consequences of changes in morbidity for women taking long term tamoxifen enabling refinement of current estimates. Detailed information will also be available on serious adverse consequences of the drug and specific side effects.

Breast cancer is a major public health problem. It is the most frequent malignancy and the leading cause of death from cancer for women over the age of 35 in the UK as well as the rest of Western Europe and North America[3]. The major known risk factors associated with breast cancer include reproductive factors and family history[4]. Since these are not easily amenable to modification by behavioural or lifestyle interventions

the emphasis for reducing the burden of mortality and morbidity from breast cancer has focused on early detection and treatment, and palliation of advanced disease.

Until recently, the impact of therapeutic interventions on population mortality from breast cancer in England and Wales has been slight with mortality rates continuing to rise. The steady upward trend in mortality from breast cancer is however beginning to reverse as more systematic efforts are made to implement effective diagnostic and therapeutic interventions and with possible changes in the distribution of risk factors in younger cohorts in the population [5,6].

Interest in chemoprevention of breast cancer has been stimulated by good evidence of a decrease in contralateral breast cancer incidence following use of tamoxifen in adjuvant therapy and the increasing understanding about the role of available oestrogen and other growth factors in the aetiology of breast cancer[7]. A number of trials are underway to investigate the impact of use of tamoxifen on incidence and mortality from breast cancer in women at high risk for the disease [2,8,9]. Risk assessments are based on family history or a summary score of reproductive factors.

The largest of these trials, NSABP P-1 has published findings of a reduction in incidence of about 50% for women at increased risk of breast cancer. Though these results have not been replicated in smaller trials published subsequently, the findings from NSABP P-1 do seem to be robust. They are internally valid and are consistent with findings by the Early Breast Cancer Triallists Collaborative Group[7]of a preventive effect of tamoxifen, reducing by 47% the incidence of cancer, in the contralateral breast for women taking adjuvant tamoxifen. The lack of confirmatory results in the smaller trials may be due to a younger population, to poor compliance in one of the studies and to differences in the risk profile of the populations recruited[9].

None of the trials provide reliable data on mortality. There are various possible outcomes associated with tamoxifen chemoprophylaxis for breast cancer. These include delaying or preventing the onset of disease and in reducing mortality from breast cancer. Reductions in the incidence of disease or a delay in the appearance of breast cancer may not be associated with a survival benefit though there may be a benefit in terms of shortening morbidity associated with the disease. It is likely however that the relationship between the benefit derived from breast cancer

chemoprevention and the cost of the intervention will be sensitive to variations in a number of parameters. These will include the magnitude and duration of the intervention, reduction in risk of breast cancer and breast cancer mortality rates. The outcome cost per life years gained estimated in this thesis will be sensitive to breast cancer free life years. The emphasis on mortality in deriving an appropriate outcome measure allows comparison with other studies of cost effectiveness. At this stage empirical information is available only on incidence. Long term follow up will be needed in fully determining the value of this intervention in relation to alternative health outcomes.

Published breast cancer chemoprevention trials have to date provided some information on the side effects of long term use of tamoxifen in healthy women though none has quantified the potential benefits of the intervention in relation to the risks of increased morbidity or mortality from other conditions or the economic costs of the intervention. Even where tamoxifen chemoprophylaxis for breast cancer is shown to be effective it may not be cost effective particularly if associated with increased resource use required to manage side effects or because of possible changes to quality of life. Indeed the cost of targeting an eligible population and administering prophylactic tamoxifen may be substantial. A small proportion of the total population is at high risk of breast cancer yet the number of women at increased risk is large with the possibility of profound effects on the use of health care resources.

As discussed earlier, the main focus of this study is to determine the cost effectiveness of tamoxifen chemoprophylaxis for breast cancer and to understand how important the main costs are in offsetting the potential benefits of the intervention. Preliminary studies have suggested that a reduction of less than 1% in quality of life could offset potential survival gains[10]. Other commentaries on this subject have concluded that there may be only a small potential gain in survival in relation to adverse effects such as increased risk of thromboembolism and endometrial cancer[11] or a substantial overall cost of service delivery where the acquisition costs of tamoxifen are high[12,13]. Without a full cost effectiveness analysis it remains unclear at what level of use tamoxifen chemoprophylaxis could produce sufficient benefit to cover the cost of service delivery or indeed generate cost savings within the health service.

The information needed for the cost effectiveness analysis covers three broad categories of resource use. Firstly, there are the costs involved in delivering a service for prophylactic tamoxifen. This includes the costs of identifying and targeting women with sufficient risk of breast cancer to be eligible for prophylaxis and the cost of running clinics for administering the drug and for monitoring and follow up.

Secondly there may be resource implications arising from changes in the pattern of use of health services because of adverse or indeed beneficial effects of long term use of tamoxifen. This requires information on changes in the use of hospital services, visits to general practitioners and use of medications by women taking tamoxifen.

Thirdly information is needed on the costs incurred by the women themselves in attending clinics or health centres to receive tamoxifen or for a follow up visit. These personal costs include the cost of travel, the cost of time off work and other costs involved as well as changes in the quality of life of women taking long term tamoxifen.

Collecting information on resource use within the context of a randomised trial is of considerable value since data can be compared directly between the 2 arms of the trial. For the cost effectiveness analysis, information collected from women recruited to IBIS on the use of resources is combined with standard unit costs for elements of service delivery, treatment, drug use or for the women's personal costs in order to estimate the marginal costs of tamoxifen chemoprophylaxis for breast cancer. The costs are applied to the resources used differently between the 2 arms of the trial using Healthcare Resource Groups (HRGs) [14] for the pattern of use of health services including the cost of mammography, the British National Formulary (BNF) [15] for use of medications - including the cost of tamoxifen in the UK and staffing costs principally for the assessment of service delivery. The cost of breast cancer is estimated from an analysis of resource use based on the findings of the Thames Cancer Registry (TCR) Audit of Breast Cancer in North Thames[16]. For each category of resource use comparison is made for the purpose of validating the data where possible with routine sources of information for the general population.

Because as yet there is no reliable information on the impact of tamoxifen chemoprophylaxis on mortality the initial assessment of cost effectiveness is based on cost per breast cancer prevented. A more useful measure for comparison with other cost effectiveness studies is the cost per life year gained. For this analysis net incidence is estimated from the results of NSABP P-1 for the potential impact of tamoxifen chemoprophylaxis within a cohort of women at high risk for breast cancer. Projections of survival benefits are included in the sensitivity analysis. The effects of discounting future costs and benefits are examined using a baseline discount rate of 5%. This was chosen over higher rates to avoid unduly minimising the impact of a preventive intervention[17,18,19].

The impact of changes in a number of aspects of resource use on cost effectiveness is also assessed in the sensitivity analysis. They include the cost of service delivery, the risk status of the women, changes in morbidity and the personal costs borne by the women themselves.

The detailed analysis presented here is unique in studies of breast cancer chemoprophylaxis since it provides an examination of the resource consequences of changes in morbidity for women taking tamoxifen prophylaxis and measures both changes in quality of life and personal costs of the intervention to the women themselves. The findings have important implications for the use of breast cancer chemoprevention with tamoxifen or its derivatives.

A full understanding of the potential role of tamoxifen chemoprophylaxis for reducing the burden of breast cancer must be considered against the background of current interventions for reducing mortality and morbidity from breast cancer and within the context of changing trends in incidence and mortality. These aspects of the study are considered in Chapter 1 with further discussion made in Chapter 7 within the context of the conclusions on cost effectiveness of tamoxifen chemoprophylaxis.

Chapter 2 reviews the evidence underpinning the rationale for tamoxifen as an agent for chemoprevention of breast cancer assessing also the potential side effects of the drug based on evidence mainly from adjuvant studies though including some work

from prevention trials. Chapters 3, 4, 5 and 6 analyse the resource use involved in tamoxifen chemoprophylaxis needed for the cost effectiveness analysis.

Chapter 3 sets out findings from a study of the costs of service delivery for tamoxifen chemoprophylaxis based on the model of delivery used within IBIS but discussing also other possible options for safe and effective service delivery including care in general practice. Chapters 4 and 5 provide an analysis of the resource consequences of changes in the morbidity of women taking tamoxifen chemoprophylaxis measured through changes in use of hospital services and use of medications respectively. Chapter 6 sets out the results from the study of health status and quality of life for women in the 2 arms of IBIS and includes the results of the analysis of personal costs borne by the women themselves.

Finally, in chapter 7 the costs of tamoxifen chemoprophylaxis including the costs of service delivery, the costs of morbidity and the personal costs to the women themselves are combined and set alongside information on effectiveness derived from IBIS and from the NSABP P-1 study to produce a consolidated estimate for cost effectiveness.

Much of the information used in this thesis is derived from collaboration with Professor Jack Cusick and his team at the International Breast Cancer Intervention Study (IBIS). In Chapter 3 details of the pattern of work and models of service delivery were developed entirely by the author through site visits and interviews with study co-ordinators in each centre. In Chapters 4 and 5 information for the economic analysis of tamoxifen chemoprophylaxis for breast cancer was derived from data collected within the protocol for IBIS designed and run by Professor Jack Cusick and others at the Imperial Cancer Research Fund (ICRF). The questions used to elucidate resource use within the study – those concerned with the rate of use of hospital services and the use of medications by women recruited to the trial – were added to the trial protocol with the help of Professor Charles Normand at the London School of Hygiene and Tropical Medicine. Extraction of data needed for the analysis was undertaken by Dr Rob Edwards, senior statistician responsible for data collection in IBIS. Accuracy and validation of the data used, its analysis and the conclusions drawn are entirely the responsibility of the author. The author developed the self-

completed questionnaire used in Chapter 5 to gather information concerning the quality of life and personal costs of IBIS to the women themselves. Clare O'neill the co-ordinator of IBIS also contributed questions to the questionnaire seeking views from the women on their personal involvement in IBIS, their understanding of breast self care and satisfaction with services for breast cancer. Analysis and discussion of these latter questions is not included in this thesis. The questionnaire was piloted in collaboration with Clare O'neill, mailed to the women in the study from the IBIS office with data entry completed by the IBIS data clerks. The analysis and conclusions drawn were the responsibility of the author. Chapter 7 draws on information developed by the Thames Cancer Registry Audit of Breast Cancer in order to derive an estimate of the current average cost of breast cancer care for use in estimating cost effectiveness of tamoxifen chemoprophylaxis. Drafts of the thesis were commented on by the advisory panel including Dr Jack Cusick at ICRF, Professor Klim Mcpherson and Professor Charles Normand at the London School of Hygiene and Tropical Medicine.

Chapter One

Background and Literature Review

The context for chemoprevention: Trends in incidence and mortality

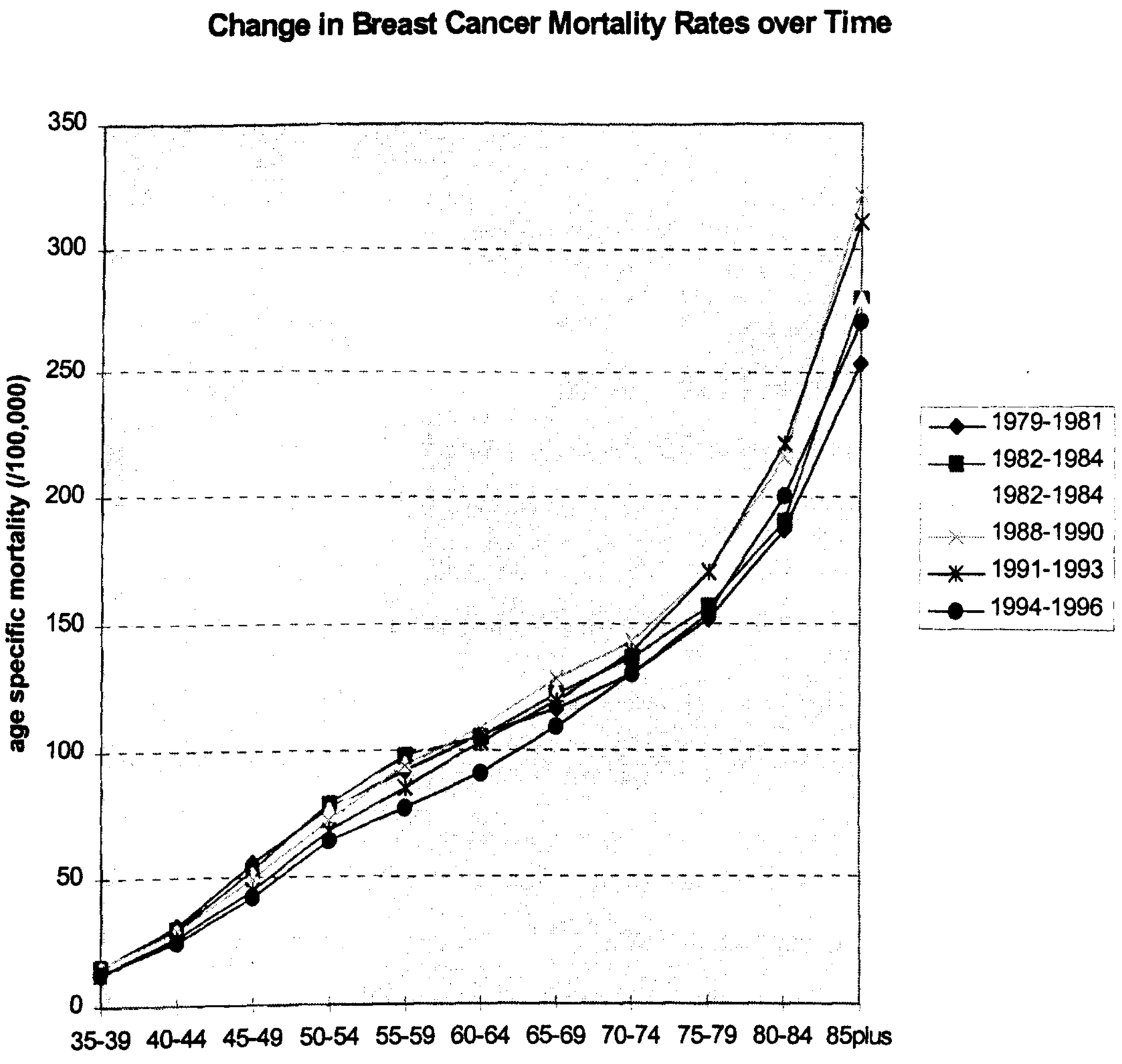
This chapter sets out the context for tamoxifen chemoprophylaxis of breast cancer. The possible impact of a preventive intervention for women at high risk for breast cancer is assessed against the background of recent trends in incidence and mortality of the disease. The scope for prevention is compared with current options for reducing mortality and morbidity from breast cancer. These include treatment of early breast cancer, interventions used in treating advanced disease and findings from the population based mammography screening programme. The prospects for primary prevention are included focussing particularly on the limited evidence available of a possible role for dietary fat.

The crude mortality from breast cancer for England and Wales (1996) is 70 per 100,000 women. There are about 25,000 new cases of breast cancer per year in England and Wales and 12,000 deaths[20]. A reduction in mortality of 35% from breast cancer as heralded for chemoprevention by some authors would have substantial public health significance potentially reducing the death rate to around 40 per 100,000 per year preventing more than 5000 deaths per year[1]. Such a broad scale improvement is unlikely from tamoxifen chemoprophylaxis however since the intervention is aimed at high risk women in the age range 40-65 while over 60% of breast cancer deaths are in women aged 65 and over.[6] Moreover a reduction in breast cancer mortality in the younger age range may have the effect of delaying rather than preventing mortality overall.

Trends in mortality

Figure 1 shows the changes in mortality from breast cancer for women in 5-year age bands including death rates up until 1996 from 1979. The data on which the chart is based are shown in Table 1. Reduction in mortality can be seen in women in the middle age range particularly from age 45-49 up until aged 60-64 where the downward trend appeared later from the mid 1980s. The trend is also evident though not as striking in women aged 65-69 and 70-74.

Figure 1



Data in Figure 1. from Breast cancer Deaths in England and Wales in 5-year age bands from 1979-1996 (using ICD9 code no 174). Published by ONS Mortality Statistics Section. Population figures for England and Wales ONS[20].

Table 1. BREAST CANCER DEATH RATES per 100,000

					5 year age bands						
Time Period	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85plus
1979-1981	15	31	55	77	92	106	116	130	152	187	253
1982-1984	15	30	53	78	97	105	122	137	157	191	280
1982-1984	15	29	51	76	94	115	123	146	170	216	280
1988-1990	15	29	50	72	94	109	128	143	170	216	322
1991-1993	13	27	45	68	85	103	120	138	170	222	311
1994-1996	13	25	42	64	77	90	109	130	154	201	271

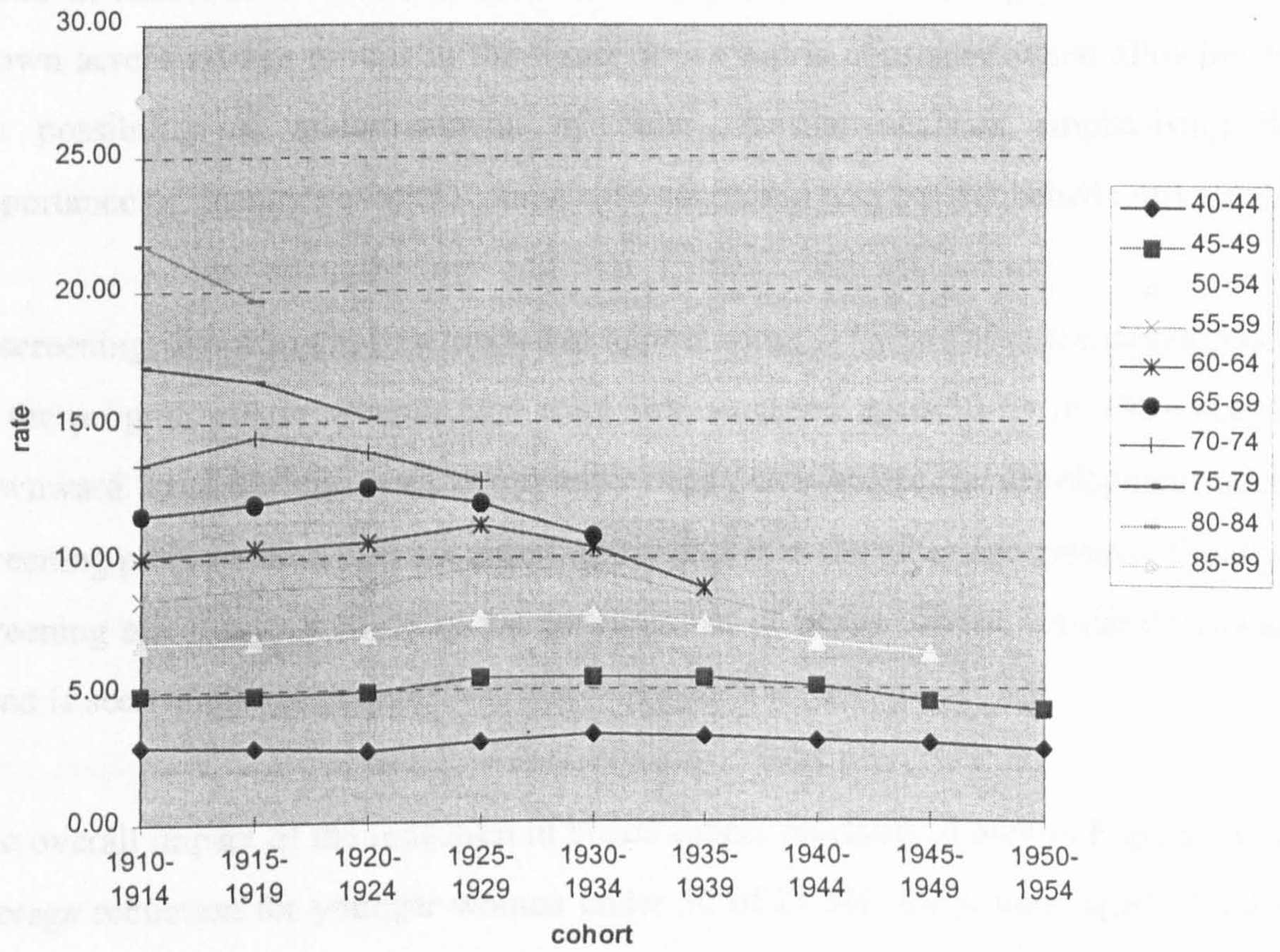
The rate of decline in mortality in the UK has been less than that seen in the recent downward trends or levelling of previously upward trends seen in many other countries world-wide particularly Australia, Austria, Canada, FRG, Greece, The Netherlands, Sweden, Switzerland and the USA[5]. Mortality from breast cancer in the UK remains the highest amongst comparable countries in Western Europe, USA, Australia and New Zealand. The decline in overall mortality in England and Wales began around 1985 following declines in the early 1980s in many comparable Western European countries[6]. An overall increase in mortality from breast cancer began in the post war years but was predominantly in the 50-54 year olds with increases in mortality for women aged 60-64 not occurring until the 1960s or the 1970s for older women. By the mid 1970s, mortality had begun to fall in women under 50 but was still rising in those over 60. For women aged 55-69 mortality rose from about 83 per 100,000 in the early 1960s to level off at around 107 per 100,000 in the mid 1980s. Though changing very little during the late 1980s mortality in this age group fell steeply after 1990 and in 1994 was 12 % lower than in 1987.

For women aged 40-59 the decline in breast cancer mortality has been linked to increased fertility during the post war years. Beral has suggested that the reduction in

mortality is due to a change in the risk profile for women because the average age at first birth and the proportion of childless women declined after the Second World War[6]. Other authors have concluded that the trends may also be due to improvements in survival because of earlier detection of tumours[21] and better treatment regimen[22]. The extent to which the decline in mortality has been the result of the introduction of mammographic screening in 1987 is still the subject of much debate. Quinn[5] concluded in an analysis of trends in breast cancer incidence and mortality until 1994 that the reduction in mortality is unlikely to be due to screening.

The decline in breast cancer mortality in many developed countries appears at least in part to be due to birth cohort effects or period effects[6]. Average mortality patterns conceal trends in different age cohorts of women[23]. In order to assess this effect the data in Table 1 and Figure 1 were recalculated to show mortality by birth cohort from women born in 1912-1916 to 1952-56 from age 40-44 to age 85-89. The results are shown in Figure 2.

Figure 2. Mortality rate (per 100,000) by birth cohort



An upward trend in mortality continued for women until the birth cohorts born in the 1930s for the age groups 40-54. These women would have experienced their peak fertility in the 50s and 60s not delaying child bearing unlike earlier cohorts who were reaching their 20s and 30s in the war years. A peak in trends in mortality is seen for women aged 55-59 born in earlier birth cohorts (1925-1929) and for women aged 60-64 for birth cohorts born in the 1920s. Younger women aged from 40-44 to 50-54 born in the 1930s see a reduction in mortality at an average of 20%. Similar reductions are seen in the older age groups though these appear earlier from birth cohorts 1925-1929 for women aged 55-59 and from birth cohorts 1920-1924 for women aged 60-64.

These data are consistent with the hypothesis that widespread improvements in treatment for breast cancer rather than the screening programme underlie recent reductions in mortality. The effects are consistent across all age groups and not seen only in the screened age groups. The drug tamoxifen was introduced into breast cancer treatment regimen in 1973 and has been shown in successive large-scale studies to increase survival for women of all ages[24]. The rate of reduction in mortality found in randomised controlled trials is around 50%. This is higher than the 20% shown across all age groups in the figure above but is consistent when allowing for the possibility of undertreatment of older. A meta-analysis emphasising the importance of treating younger women with tamoxifen was not published until 1998[7].

A screening effect might be expected to appear some 5-7 years after the development of the programme for women who were first screened aged 50-54 in 1987 but the downward trend in breast cancer mortality began well before the development of the screening programme and is not significantly higher in the older age groups. Finally a screening effect may well delay the development of breast cancer, yet the downward trend is seen in all age groups.

The overall impact of the reduction in breast cancer mortality shown in Figure 2 is an average reduction for younger women under 50 of 21.5%, for women aged 50-64 of around 33% and for women over 65 of around 12 %. For women in the age group

targeted for tamoxifen prophylaxis (45-64) the reduction in breast cancer mortality rates since the mid 1980s represents about 1000 breast cancer deaths prevented per year (assuming a rate of around 84 per 100,000 and 12,000 deaths per year for this age group in the mid 1980s compared with a rate of around 68 per 100,000 in the most recent figures).

Chemoprevention with tamoxifen by contrast would be targeted at only a proportion of these women though the mortality reduction is estimated to be greater. Comparing the same population with the rates prevailing in the mid 80s and assuming that chemoprevention is targeted towards one third of all women with an efficacy of around 33%[25,26] the numbers of breast cancer deaths prevented might be less than half of those actually seen from changing trends in breast cancer mortality. Clearly the costs in terms of the disbenefits of the intervention need to be considered carefully in fully evaluating the effect. The potential for enhancing the downward trend in breast cancer mortality is considerable. Careful analysis will be needed to fully evaluate the effect against the current improving trends in breast cancer mortality and the further potential for more appropriate application of adjuvant tamoxifen.

Trends in Incidence

The incidence of breast cancer in the female population in the UK increased by about 2% each year from the late 1950s to the late 1980s. From 1988, after the introduction of the screening programme the annual rate of increase more than doubled to nearly 4.5% until 1991; there was virtually no change in incidence between 1991 and 1992. In 1992 the age standardised incidence of breast cancer in women in England and Wales was 102 per 100,0000 about a 40% increase from 74 per 100,0000 in 1974[27].

Age specific incidence rates for breast cancer rise rapidly with age though unlike other common cancers the rate of increase declines after age 50 around the age of the menopause. Currently approximately one in 14 women in the UK will develop breast cancer by age 75. A similar pattern in incidence of breast cancer is seen in other Western European countries[28].

Table 2 shows the lifetime risk of breast cancer (Cumulative incidence (%)) in 1992 for the most recent data available, in 1987 at the time of the development of the NHS Breast Screening Programme and in 1982 prior to the introduction of the breast screening programme.

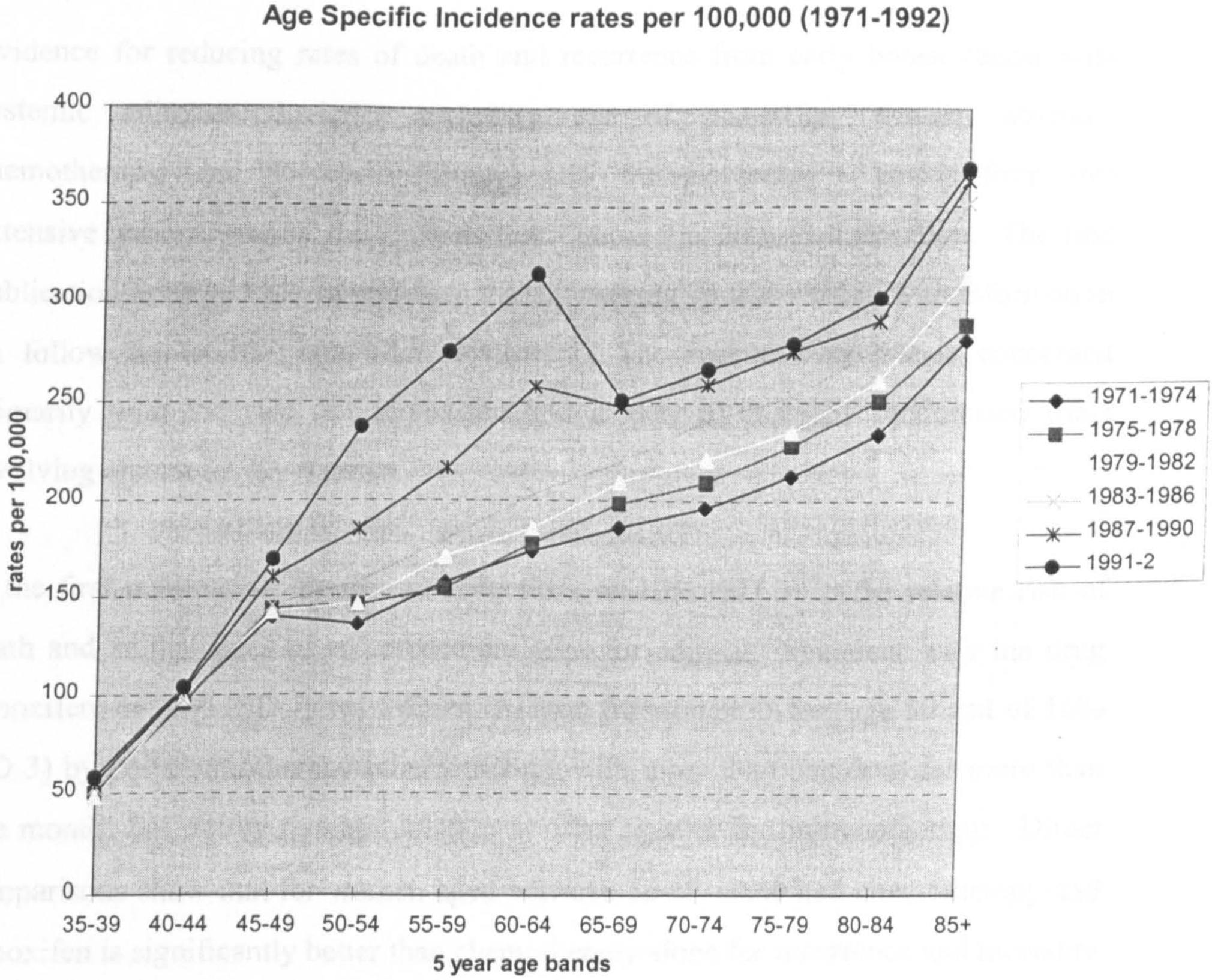
Table 2: Lifetime risk of Breast Cancer (cumulative incidence) in 1982 and 1992.

	Rate per annum		Rate over 5 years		Cumulative Incidence	
	per 100,000		per 100,000		(%)	
Age group	1982	1992	1982	1992	1982	1992
30-	25	30	125	150	0.1	0.2
35-	50	50	250	250	0.4	0.4
40-	100	100	500	500	0.9	0.9
45-	150	175	750	875	1.6	1.8
50-	150	240	750	1200	2.4	3
55-	175	250	875	1250	3.3	4.2
60-	190	265	950	1325	4.2	5.6
65-	200	265	1000	1325	5.2	6.9
70-	220	270	1100	1350	6.3	8.2
75-	225	300	1125	1500	7.4	9.7
80-	250	300	1250	1500	8.7	11.2
85-	300	330	1500	1650	10.2	12.9
90-	310	360	1550	1800	11.7	14.7
95-	320	400	1600	2000	13.3	16.7
Based on Age specific incidence rates per 100,000						

The table shows the lifetime probability of acquiring breast cancer for women in each age category according to life expectancy. For women aged 30 the life expectancy is 83 years. Reading against the 80- category shows that the probability of acquiring breast cancer has risen from 8.7% (1 in 11) in 1982 to 11.2% (1 in 9)in 1992. If the women lives longer then the rate increases to 12.9% (1 in 8) by age 85 assuming that the 1992 incidence rates continue throughout her lifetime.

The impact of the NHS Breast Cancer Screening Programme on registration rates can be seen clearly in Figure 3. Age specific incidence rates for breast cancer are plotted for cohorts of women by 5 year age groups.

Figure 3.



Female breast cancer (ICD9 174), England and Wales, 1971 to 1992

* Cancer statistics - registrations, Series MB1 no.23 1990, ONS (1997)[27].

** Registrations of cancer diagnosed in England and Wales, Monitor MB1 96/1, ONS (1996) (provisional result

\+ Directly age standardised using the European standard population.

The increase in the incidence rate of registration of breast cancer since the development of the NHS Breast Screening Programme can be seen for women aged 50-64 - the screened age group. Incidence figures are often difficult to ascertain

because of problems due to reporting error. Nevertheless the changed trend demonstrated here is likely to be due directly to early detection by the breast screening programme rather than a true increase in breast cancer risk.

Treatment effectiveness for early breast cancer: systemic therapy

Evidence for reducing rates of death and recurrence from early breast cancer with systemic adjuvant therapies including use of tamoxifen, ovarian ablation, chemotherapy (and polychemotherapy) and immunotherapy - comes from two extensive publications by the Early Breast Cancer Triallists Collaboration. The first publication reviewed 133 randomised trials involving 75,000 women with information on follow up to 10 years after treatment[24]. The second overview is concerned primarily with the role of tamoxifen and is derived from 55 randomised trials involving almost 37,000 women[7].

In the first publication, significant reductions of 17% (SD 2) in the relative risk of death and annual rates of recurrence are seen for adjuvant treatment with the drug tamoxifen, of 25% (SD 7) for ovarian ablation for women below age 50 and of 16% (SD 3) by polychemotherapy (chemotherapy with more than one drug for more than one month) but not by ovarian ablation at older ages or by immunotherapy. Direct comparisons show that for women aged between 50-69 combined chemotherapy and tamoxifen is significantly better than chemotherapy alone for recurrence and mortality ($p<0.00001$) and for tamoxifen alone for recurrence ($p<0.000001$). Estimates suggest a reduction in the risk of death of around 30% (SD 4) for combined chemo-endocrine therapy for women in the 50-69 age group. The proportional risk reduction will be about the same for node positive and node negative women though the absolute improvement in 10 year survival is twice as high for node positive women because of their relatively poorer prognosis.

For women under 50 only 2 treatments have clearly significant effects. These are a 27% reduction in the relative risk of death following chemotherapy (SD 6) and a 28% reduction following ovarian ablation (SD 9). Indirect comparisons alone showed a

significant benefit from combining chemotherapy and ovarian ablation. Both direct and indirect randomised comparisons showed polychemotherapy to be significantly better than single agent chemotherapy at any age; polychemotherapy has a greater impact on the risk of death for younger women, a 25% (SD 5) reduction in the relative risk of death for women under 50 compared with a 12% (SD 4) reduction in relative risk for women over 50).

The effects of tamoxifen appear to be cumulative. Most of the regimen included in the studies were for a median of 2 years for tamoxifen and 1 year for polychemotherapy yet significant differences in survival between treated and control groups were found at both 5 and 10 years. The collaboration demonstrated a highly significant trend towards a greater therapeutic effect for longer-term use of tamoxifen although the directly randomised comparisons of different tamoxifen duration indicate only a non-significant difference in favour of long term therapy. These results were confirmed by the second overview which found that in oestrogen receptor women or in those where the oestrogen receptor status was unknown for women treated with tamoxifen for one, two or five years the reduction in the rate of recurrence was 21%, 29% and 47% respectively. The reduction in contralateral tumours was 13%, 26% and 47% and the reduction in mortality was 12%, 17% and 26%. The number needed to treat (NNT) to prevent recurrence for women treated with tamoxifen for five years was eight. Further evidence also emerged in the second overview on the benefits for younger women of about five years of tamoxifen adjuvant therapy with an absolute reduction in recurrence rates as a first event of 14%.

It is important also to note in these studies that the incidence of endometrial cancer was shown to double after 1-2 years of tamoxifen use and to increase four fold in trials of five years or more of tamoxifen. The absolute reduction in the risk of contralateral breast cancer is however about twice as large as the increase in the incidence of endometrial cancer. There was no apparent increase in the incidence of any other cancer although ascertainment of death was not complete. Overall there was a relative reduction in the risk of death from all causes for women in the intervention group compared with control (rr=0.99 SD 0.05).

Treatment of Advanced Disease

There are no standard therapies for second or third line treatment for patients with refractory disease or with anthracycline resistant metastatic breast cancer or for patients with high-risk presentations of early disease. Yet, given the prevalence of the condition and the poor prognosis for newly diagnosed women with extensive axillary node involvement and late stage disease in general there is a good deal of interest in developing new drugs to improve outcome.

Claims are made for the efficacy of some agents such as docetaxel (taxotere) as a unique agent in the treatment of metastatic breast cancer and use of this drug is increasing. The evidence for efficacy of the drug is mostly from case series (so called phase 2 studies) designed to test the likely magnitude of response of the drug and to monitor the side effects and a limited number of randomised controlled - phase 3 drug trials. A review of phase 2 studies report a total of 317 patients observed in 8 different studies throughout Europe, North America and Japan[29]. Excluding the Japanese study which had 85 people entered and offered a lower dose of docetaxel than in the majority of the other studies, the mean number of women observed was 33. The range of response to treatment in these studies lies between 39 and 57% with docetaxel used as first line therapy in four studies and second line chemotherapy in three studies. Few patients achieve complete response in any of the studies. Complete response is defined as the disappearance of all clinical evidence of tumour by physical examination or imaging studies for a minimum of four weeks. Most reports are of partial response defined as broadly a 50% reduction in the sum of the bi - perpendicular diameters of all neoplastic lesions for at least four weeks.

Phase 2 studies are not controlled studies; response rates, mean duration of response and survival rates can only be compared within the study among patients who responded and those who did not. Many of these case series report a high number of patients experiencing significant side effects or progressive disease leading them to withdraw from treatment; a large proportion of patients also experience dose

reduction. The results of the phase 2 studies are broadly similar and a more detailed examination of the two most recent is considered below.

In two Phase 2 studies[30,31] from North America published in the last three years patients with metastatic breast disease treated with docetaxel as second and first line therapy respectively achieved remission in 53% and 54% of cases. In the patients treated first line there was complete response in two (5%) out of the 37 patients treated and a partial response in 18 (49%) patients. The median response duration was 26 weeks, excluding four patients who withdrew from the study while in response in order to receive high dose chemotherapy. In the study of second line therapy 18 out of 35 patients achieved a partial response. The median response duration was 7.5 months (30 weeks) with an overall survival for responding patients of 13.5 months. The median overall survival rate was nine months for all patients entered into the study. No information is given in either paper to compare the outcome with the median survival of patients treated on standard palliative therapy

Of the toxicity reported, neutropenia is the most usual dose-limiting problem. In the first of the studies described above 31 out of 35 patients are reported to have had neutropenia 18 of which were complicated by fever mostly requiring intravenous antibiotic; eight of these patients also contracted significant infections, one patient died. In the second study 35 out of the 37 patients experienced neutropenia and leukopenia and there were 19 episodes of febrile neutropenia. Infection was documented in six of these patients. One patient with neutropenia developed mucositis with gastrointestinal haemorrhage and died. Myelosuppression and alopecia are also usual while nausea and vomiting are less so. A high proportion of patients in both studies (33 out of 35 and 30 out of 37 respectively) experienced fluid retention. In the latter study 30% of patients withdrew because of this toxicity. The aetiology of fluid retention for patients taking this drug is poorly understood and may limit implementation.

A randomised phase 3 trial completed on a sample of 392 patients in N. America[32] found a significant improvement in response rate for patients with anthracycline

resistant disease randomised to receive docetaxel compared with those on Mitomycin C plus Vinblastin. Response rates in the docetaxel group compared with standard therapy were 30% compared with 11.6%, time to progression was 19 vs11 weeks and overall survival was 11.4 months compared with 8.7 months .

Costs involved in administering docetaxel are significant since a high proportion of patients will experience significant side effects, some of which require in patient hospital treatment. Moreover, anticipated sensitivity reactions are treated in advance with steroids or antihistamines. Treatment costs alone to achieve the three months survival benefit rate reported in the phase 3 randomised trial per patient benefiting would be around £50,000 since the data suggest an NNT of 5.4 and costs per patients for the drug alone are around £9,000.[32/1, 32/2]

Bone Marrow and Peripheral Blood Stem Cell Transplantation for Breast Cancer

The partial success of adjuvant chemotherapy in the treatment of metastatic disease alongside evidence for a dose response effect of chemotherapy in both early stage disease and in patients with metastatic disease provides the clinical rationale for research using intensive high dose therapy (including myeloablative chemo and radiotherapy treatments together with progenitor cell transplantation) in patients with high risk presentations of early stage disease. Moreover, the toxicity associated with high dose therapy has been substantial and has constituted a considerable barrier to its use for women with breast cancer. More recently, however, advances in treatment have reduced the mortality (to below 5%) and morbidity of treatment enabling greater experimentation with intensive therapy and the prospect of widespread use of active treatment in advanced disease. High response rates have been found in some series though the duration of the effect has been limited.

To date there have been only three randomised trials of high dose therapy compared with conventional chemotherapy including a total of 197 patients. One of these trials used high dose chemotherapy with hematopoetic rescue as a primary treatment. In

the other two trials initial chemotherapy had been given though in one of these studies only nine patients were randomised restricting meaningful analysis. This latter small study reported a significant benefit for patients on conventional therapy though presented little information on survival and stopped early because of poor recruitment. The remaining trial found a significantly increased odds ratio for survival in the experimental arm.

A review of high dose therapy[33] suggested that the limited evidence from randomised trials is inconsistent. The trial reporting a benefit when treating patients with primary disease may be confounded by tamoxifen given as maintenance therapy to patients responding to high dose regimen. Patients receiving conventional chemotherapy were less likely to respond to treatment and so fewer also received tamoxifen. Moreover patients in the control arm had a lower survival rate than expected by comparison with other series. The trial showing an advantage for patients on conventional chemotherapy also showed a significantly higher survival rate for patients given high dose therapy. The results in this case may well have been affected by patients in the conventional arm crossing over to receive high dose therapy at the time of recurrence. Clearly further studies are needed before treatments of this kind can have any role in conventional care of breast cancer.

Cost effectiveness of treatment for early breast cancer

Few studies are available to assess fully the cost effectiveness of current interventions in breast cancer. Results from the overview[5]discussed above were however used to estimate the comparative costs involved in following alternative treatment regimes in adjuvant therapy for early breast cancer. The costs were applied to the standard cyclophosphamide, methotrexate and flouracil regimen (CMF)[34] for chemotherapy and for antiemetics, administration costs, supplies, blood cell counts and medical time and were compared in relation to the benefits (numbers needed to treat) with the addition of tamoxifen for both two and five year regimen. The costs are based on

estimates of standard polychemotherapy and tamoxifen and include antiemetics, other supplies, blood cell counts and doctor time.

The results for women treated in the USA show that systemic therapy is highly cost effective. The costs per life saved at ten years in early breast cancer ranges from around $17,000 for women at all ages in the highest risk category to over $50,000 for women at any age at a lower risk of death. Where the duration of treatment is increased or where combined therapies are used costs increase substantially. The cost of treatment with tamoxifen is less in the UK now that patent restrictions no longer apply to the drug. Costs of tamoxifen in the UK are around £30/patient per year and of standard polychemotherapy around £300 for a single cycle of treatment.

The cost effectiveness of adjuvant therapy is proportional to the individual risk. Cost per QALY estimates for women under 50, for example vary with oestrogen status from $12,000 for node negative oestrogen receptor positive breast cancer to $4000 and $6,000 for node positive breast cancer in pre and postmenopausal women respectively. For postmenopausal women with node negative breast cancer cost per QALY estimates vary from $28,000 – 36,000[35]. The Early Breast Cancer Triallists Collaboration[7] concluded that the treatment of low risk patients was as effective and that the addition of combined therapies offered moderate additions in life expectancy. Yet these strategies are unlikely to be as cost effective as targeting and treating women in higher risk categories. Similar effects would be seen with the effect of dose where increased or changed regimen may increase costs considerably for small reductions in mortality or risk of recurrence. Very little information is available on the impact of changes in quality of life for alternative treatment regimen in breast cancer care yet this may affect the balance of costs and benefits quite considerably. Most estimates of the cost effectiveness of treatment options are made on the basis of mortality reduction alone.

Quality of care

As discussed earlier the incidence of breast cancer in the UK though high is comparable to that of other western European countries yet the mortality rate has remained consistently higher. Studies in the UK continue to show variations in the management of patients with breast cancer despite adjustments for case mix both in the North East and South East of England[36,37]; variations in health outcome between Health Authorities have also been well documented[38]. The Eurocare study[39] providing the largest set of population based estimates of cancer survival in 12 European countries shows considerable variation in age adjusted survival for women diagnosed with breast cancer using data from 30 cancer registries between 1978 - 1985. In particular the study found that women in England and Wales faced lower prospects for survival than women in most other comparable countries. Compared with 62% 5-year survival for women in England and Wales, only 2 other of the countries studied, Estonia and Poland, had poorer survival rates. Survival in Scotland ranked 8th equal with a survival rate of around 65%. The authors claim that with implementation of effective practice throughout the UK further reductions in mortality of at least 10% could be achieved.

Although guidelines for optimal management of breast cancer are now available[40,41] variations in management and use of poorly evaluated treatments persist across the UK[42]. The average 5-year relative survival rate for breast cancer in England and Wales remains between 60 and 65% and the median survival is just over 8 years[43]. Data from the Scottish cancer registries analysing survival rates among 34,107 women with breast cancer diagnoses between 1968 and 1987 did show improvements in 5 year survival rates particularly for women under 55 (10%) compared with women aged 55-64 and 65-74 (9% and 6% respectively)[44]. Gillis and Hole[44] argue that this was due to a range of therapeutic advances including more widespread use of chemotherapy and radiotherapy, the emergence of multidisciplinary breast cancer teams and increasing specialisation of breast cancer surgeons as well as the introduction of tamoxifen.

A more recent audit from the Scottish Cancer Therapy Network suggest that improvements in the quality of care are possible where patients have access to breast specialists[45]. Between 1987 and 1993 the proportion of patients having surgery to the axilla had increased and the proportion of patients receiving systemic adjuvant treatment had increased. The 5-year survival was 9% higher and the 10-year rate 8% higher for patients treated by specialist surgeons than those treated by general surgeons. When the results were adjusted to account for the case mix of patients in the different centres the reduction in the risk of dying for patients in specialist centres increased to 16%. The benefits of specialist care were found across all subgroups examined including patient's age, the size and stage of tumours and patients from different socio-economic groups[46].

Breast Screening

The NHS Breast Screening Programme (NHS BSP) became fully operational in the UK in 1988 following publication of the Forrest Report[47]. which recommended routine mammography screening every 3 years for women aged 50-65. The policy was adopted by the NHS and led to the development of 99 screening units throughout the UK operating a mobile screening service with a computerised call recall system for the relevant age group at an estimated cost of £38m. Women are called via their GP once every 3 years; results are usually posted within 2 weeks of screening. Women with positive or equivocal results are recalled for assessment to the breast-screening unit. Diagnostic assessment of non-palpable lesions is carried out using triple assessment: clinical examination, further mammography and core biopsy or fine needle aspiration, the latter is more usual for palpable lesions.

The rationale for the programme was based on a number of trials particularly those published from Sweden which showed a beneficial effect of screening mammography especially in the 50-64 age group[48]. An overview of the Swedish trials[49] undertaken in two counties and three cities and including 156,111 women in the invited group compared with 125,866 in the control group showed an estimated overall reduction in mortality of 24%; this was 6%, 28% and 34% in the age groups 40-49,50-59 and 60-

69 respectively. The cost effectiveness estimates for the programme were based on single medio lateral oblique view mammography and a target uptake of 70%.

The NHS Breast Screening Programme is now in its 3rd round. Uptake rates are variable throughout the country though the overall rate of 72% uptake achieved in 1990-93 has been exceeded with uptake rates of 77.4% in 1994-5. Regionally the uptake varies from just under 70% in the Thames Regions to over 80% in East Anglia, Oxford and Wessex[50]. The programme has exceeded the early cost estimates which now stand at nearer £45m/year[51]. Increased expenditure will be needed with the demographic increase of women in eligible age groups.

Subsequent trials of breast screening efficacy have however been equivocal in supporting the early estimates of mortality reduction though an overview found a 30% reduction in mortality for women in the screened age groups. The cost of the programme has risen substantially and a full evaluation is urgently needed to tackle the controversy about the value of mammography screening compared with alternative means for reducing mortality from breast cancer. The impact of the programme in the UK is low since screen detected cases still comprise around 50% of breast cancers detected in total for women in the screened age groups. As fewer than 40% of all breast cancers registered occur in the eligible age range this may limit the impact of the programme to the possible early diagnosis of only 20% of cases[52]. Proposals to increase the impact of the programme such as reducing the interval for screening, extending the programme to cover younger women or removing the upper age limit need to be assessed against the impact of the current programme on overall mortality[53,54]. Changing or extending the programme to target women at high risk of breast cancer because of family history has also been proposed[55].

Many of the criteria set out by the WHO[56] for the validity of screening programmes are met by screening for breast cancer: there is an early recognisable stage, mammography is a suitable screening method and appears to be acceptable to women, facilities for diagnosing and treating abnormal findings are available and can be monitored. Breast cancer is an important disease being responsible for a considerable

number of years of life lost since it affects women in middle age and early detection may lead to a more favourable prognosis. The natural history of breast cancer is still, however, not sufficiently well understood and it is possible that the treatment given in the early stage of the disease is not more effective than after the clinical diagnosis of symptomatic disease. Early detection will lead to an apparent improvement in survival because of lead-time bias but may not produce real reductions in mortality.

The compelling public policy questions concerning the effectiveness of age based mammography screening for breast cancer are whether the costs involved are justified in terms of reduced population morbidity and mortality from breast cancer. Measures of the effectiveness of screening programmes should include evidence of changes in population mortality as well as improvements in case survival.

Published estimates of the effectiveness of breast cancer screening programmes are available from nine randomised clinical trials of mammography in six countries. The recent trials[48,49,57] were not significant though a meta analysis did show a statistically significant relative risk reduction of 25-30% in mortality due to breast cancer for women over 50.[37] There was no effect was shown for women under 50. There is considerable debate in the interpretation of this result in terms of the expected absolute benefit for women in continuing with the screening programme and the cost per life saved in comparison with other health care interventions.

As might be expected there are a number of differences in the characteristics of the trials such as the uptake rates and the ratio of benign to malignant tumours detected. The policy of different countries also varies with regard to screening intervals, follow up, type of mammography used and the weighting given to issues such as costs involved in further investigation and treatment and the personal costs of travelling as well as reduced availability for work and incidental expenses.

A recent editorial reviewing all of the published trials of screening effectiveness suggests that the absolute benefits of breast cancer screening are small ranging from mortality reduction of 0.05 - 0.14%[58]. The number of women who need to be

screened to save one life ranges from around 7,000 to 63,000 in the screening trials. A number of authors' highlight that insufficient attention is given to the problem of false positives. About 1 in 20 women have a screening abnormality - a positive or suspicious result -but only between 1 in 5 and 1 in 14 will have cancer. These positive or suspicious lesions lead to considerable often quite invasive unnecessary further investigation and surgery. Secondly a negative result does not mean the absence of cancer since 10 -15% of early lesions are missed by screening. Finally for the majority of women in whom breast cancer is diagnosed by screening the outcome is unchanged[59].

Other authors have argued that screening is both effective and cost effective comparing favourably with other health care interventions such as renal dialysis. Estimates of the cost per death prevented range from £25,000 -£100,000 for UK women[60]. The lower range depends on detection rates of around 0.2% which is higher than the 0.06% found for example in the 1985 SNBH study[61]. Based on these studies cost per year of life saved is estimated to be around £5000; this compares with haemodialysis at £20,000 per year of life saved. Moreover some authors argue that the rate of inappropriate biopsies and other interventions in the NHS are far lower than might be expected from an analysis of practice in the USA where the pressure to intervene leads to substantially higher average costs. The benign: malignant ratio is now lower than the 4:1 expected in the Forrest report with some centres reporting 1:4[62].

Changing the age range

Recent guidance from the NHS Executive allowed women over 65 to opt to continue attending for 3 yearly screening mammography though they will not be included in the call recall system. The uptake among older women is currently the subject of evaluation. It has been estimated that extending the age range of the programme may offer an incremental increase in deaths from breast cancer prevented at a cost, which is, lower than that implicit in the current programme[63]. The current NHS breast-screening programme does not currently target women at highest risk for breast cancer

and studies have shown an advantage for women up to age 75. Mortality from breast cancer may well decline if there is systematic screening of women in older age groups though increased anxiety could also be a significant consequence of advancing the lead time for diagnosis in this age group.

Incremental cost estimates from the current NHS BSP are £25,142 per death prevented, or £2,525 per life year saved. Extending the age range to 69 years offers an incremental cost per death prevented of £21,376 or £2,990 per life year saved whereas reducing the screening interval changes the incremental cost per death prevented to £39,431or cost per life year saved £3,545; both options improve the efficiency of the current breast screening programme.

All the arguments in favour of screening younger women are derived indirectly from studies that show no advantage in the original analysis. Only one of the eight randomised-controlled trials was designed to study the effect in pre - menopausal women[64] Meta analysis showed a non significant reduction of 10-15% in women under 40[65]. In the UK, mortality from breast cancer in this age group is around 30/100,000 suggesting that at least 1,000 women would have to be screened for 16 years before saving a single life. Detectability of small lesions is more difficult in the younger breast because of the density of the tissue. Reduction in mortality for increased cost are unlikely to compare favourably with that possible for older women although it could be argued that the increase in life years gained would be considerable.

Targeting women who are most at risk of breast cancer may be the most effective way to improve the predictive value of screening and to lower the false positive rate. Between 5 and 20% of women with breast cancer have an increased relative risk because of family history or reproductive factors. A proportion of these will have the highly penetrant cancer susceptibility gene such as BRCA1 or a familial cancer syndrome. High risk women have most to gain in reduced anxiety and earlier detection; this group will experience higher absolute benefit especially younger women where the potential years of life saved are considerable[66].

As discussed earlier, an evaluation of the trends in incidence in the UK[5] following the development of the screening programme show the increases that were expected in the prevalence round. From 1979 to1987 the rate of increase in incidence was approximately 2% per year to 86/100,000. After the introduction of the screening programme the annual rate of increase more than doubled to nearly 4.5% each year to 102/100,000. The greatest increase is seen in the screened age group (women aged 50-64). Incidence rates rose and exceeded those seen in the elderly unscreened population (women over 65). As early as 1990 incidence in 60-64 year olds exceeded that of 80-84 year olds. Incidence in age groups not invited to the screening programme fluctuated only slightly throughout this period. Recorded incidence is expected to return to pre-screening levels in the screened age group after the prevalence round, except for women in the age group 50 -52 who will always be in a prevalence round.

The impact of the screening programme can also be seen in the proportion of tumours that were small and node negative. Mortality has also changed quite markedly since the beginning of the screening programme though is unlikely to be attributable mainly to it. For women between 55-69 a steep rise in age standardised mortality after the war continued until the late 80s when it fell sharply until in 1994 it was 12% lower than in 1987. Any effect of the screening programme on mortality is unlikely to be seen until at least 7 years after the prevalence round. None of the screening trials show a reduction in mortality around the period of the prevalence round.

Further evaluation of the programme is needed to address the potential for reducing morbidity for patients with earlier diagnosis of cancer prior to metastasis and the costs of care associated with earlier diagnosis. In developing a true assessment of population benefit the programme must demonstrate benefits in cost per life saved which exceed those seen with alternative means of reducing mortality and morbidity from breast cancer. The benefits of refocusing the programme to cover women at highest risk including older women and women with risk factors due to family history or reproductive history are made in comparison with the outcome from the current

programme though not in terms of alternative means of reducing mortality. At present estimates of the cost effectiveness of adjuvant therapy exceed those for breast screening by almost five fold.

Risk of breast cancer and the potential for primary prevention.

Breast cancer risk factors

Epidemiological evidence supports the hypothesis that ovarian hormones are strongly implicated in the aetiology of breast cancer[67]. Early menarche, late menopause and nulliparity are associated with increased risk. The incidence of breast cancer is reduced by oophorectomy or by induced menopause with radiation. Experimental evidence with mice shows that ovarian function or stimulation with oestrogen is required for tumour development[68]. The risk increases with length of exposure - the earlier the intervention to reduce ovarian function the greater the reduction in risk. Oestrogen alone and with progestogen induces cell division and is of considerable interest in the pathogenesis of breast cancer. Other endogenous hormones such as prolactin and androgens may also be involved though further research is needed to fully elucidate their possible role.

Family history increases the probability of breast cancer. Women with an affected first degree relative have a 2-3 fold increased risk and those with an affected second degree relative have a two fold increased risk. Risks are even further raised if two first degree relatives are involved or if the first degree relative has bilateral breast cancer or if the cancer was diagnosed before age 40[69].

Overall only around 5% of women with a family history of breast cancer have a breast cancer gene; young age at breast cancer of a first degree relative is the strongest indicator of genetic susceptibility. Other risk factors directly associated with endogenous oestrogens include reproductive factors. Late age at first full term pregnancy (30 years of age or more) and nulliparity increase risk and high parity decreases risk in women aged over 50[70].

Obesity, which increases risk of breast cancer in postmenopausal women, is thought to be linked to a hormonal mechanism. Case series and laboratory studies have shown that obese women have higher levels of serum oestrogen than non-obese women. This is because of greater metabolisation of androstenedione to oestrogen in adipose cells[70]. The extent to which body mass is implicated as a predictor of breast cancer is however complicated since overweight may reduce the risk of breast cancer in pre - menopausal women and the timing of weight change as well as the distribution of fat may also predict increased risk of breast cancer[71]. In pre-menopausal women extended breast feeding may, through suppressing oestrogen production, confer a protective effect on the risk of breast cancer but the evidence for this is not strong[72].

A meta-analysis of 27 epidemiological studies of the effect of oral contraceptives on breast cancer risk suggests that risks may be increased by about 20% for younger, nulliparous women and for long term use[73]. Likewise, hormone replacement therapy is only associated with an increased risk of breast cancer after five years of use and the beneficial effect on the cardiovascular system and on a reduced risk of osteoporosis may also outweigh the adverse effects on breast cancer risk[74].

Other known risk factors which are more amenable to change are chiefly associated with diet[75] and exercise[76]; alcohol use has also been implicated. A meta - analysis of 50 studies looking at the relationship between alcohol intake and breast cancer risk suggested a small positive association; around a 25% increase in risk with the equivalent of two drinks (two units of alcohol) per day[77]. Other studies[78] including a more recent review of the literature[79] concluded that causality had by no means been demonstrated and that several factors modify the relationship including age, weight and use of exogenous oestrogen. There are a number of measurement problems in estimating alcohol use, difficulties in detecting small relative risks and errors in confounding. Widespread changes in the use of alcohol are unlikely to have a significant effect on the profile of breast cancer especially since the publication of trials showing the beneficial effect of alcohol on HDL cholesterol and the corresponding reduction in cardiovascular risk.

Physical activity in adolescence and among young adults has been shown to reduce the risk of breast cancer in premenopausal and perimenopausal women. Risk reductions may well be hormonally mediated since physical activity delays the onset of menarche and decreases the number of ovulatory cycles[80]. Studies suggest that the effect of physical activity is independent of body size - though is difficult to separate from the effect of activity on excess body mass[81].

A great many studies have been reported which seek to explore the relationship between dietary fat and breast cancer. There is considerable debate about any possible association and the potential for primary prevention through dietary intervention. Consideration is given to this in a separate section below. A number of epidemiological studies have suggested that carotenoids in fruit and vegetables have a protective effect on breast cancer risk[82]. Other studies of specific nutrients include vitamin A from animal sources[83]. Both vitamin A and carotenoids have anticarcinogenic effects in laboratory experiments. Little confirmatory information is available.

A great deal of concern has been raised in the literature about the possible effects of environmental pollutants on breast cancer risk[84]. Some authors have suggested that women with breast cancer have higher levels of organochlorines in their serum though others have shown no association. Electromagnetic fields and ionising radiation have also been investigated. Electromagnetic fields are currently under review though the more intensive exposure through use of electric blankets is not implicated[85]. High dose ionising radiation to the chest does increase breast cancer risk at the level of dose required for radiotherapy[86].

Country of birth has a marked effect on risk of breast cancer and wide variations in incidence rates suggest there is scope for improving rates world-wide. Rates are higher in developed than in developing countries except for Japan where the rates are half those of N. America and N. Europe though they are increasing. Where women migrate, their breast cancer rates over two or three generations assume a pattern more

similar to the host country suggesting that the determinants of breast cancer risk are more likely to be environmental than genetic[87].

Scope for primary prevention

For women identified at high risk increased surveillance through screening mammography and clinical examination is available for early diagnosis. Bilateral mastectomy[80] and oophorectomy are highly effective and may be a practical option for women in high risk groups particularly those with significant family history or positive identification of breast cancer genes; doubt does remain however even with these radical procedures particularly over long term psychological sequelae and the prospect of tumours developing in the chest wall. Gene therapy may eventually be possible. For women using exogenous hormones some modification of contraceptive method may be possible after long term use and women taking HRT for longer than five years may wish to balance continued use and the potential for increased risk of breast cancer with possible reduced risk of osteoporosis and cardiovascular disease.

Well known risk factors explain a large proportion of breast cancer incidence yet there are substantial gaps in knowledge about how they might be modified to reduce the risk of breast cancer. Risk factors concerned with family history are thought to be related to or mediated by endogenous hormones and so are assumed to be not amenable to change. Yet breast carcinogenesis and the development of disease are equally complex processes and have been subject to a great many clinical trials. Prevention trials have raised greater ethical concerns.

In cancer prevention trials a great many healthy women would need to be involved to detect an effect since breast cancer occurs at a rate of between 0.5 and 0.8% in the age group which is likely to be targeted for prevention. An intervention period of several years is likely to be needed to achieve the required endpoint and any trial would involve considerable cost in order to achieve the power needed to detect an effect. Such considerations may have contributed to the dearth of cancer prevention trials

though it is surprising that even for risk factors which could be modified through lifestyle change such as obesity, changes in alcohol intake or contraceptive use our understanding of their impact is almost entirely based on observational data from analytical epidemiology.

Given the impact of obesity on breast cancer risk it is surprising that weight reduction in obese postmenopausal women and weight reduction in middle age is not explicitly examined in health promotion trials. Alternative means to increase exercise among young women may also merit further research. A randomised controlled trial will determine if dietary interventions with a vitamin A derivative will affect the rate of recurrence of breast cancer in women with previously diagnosed disease or the incidence of breast cancer in the contralateral breast[89].

A large randomised trial of dietary intervention is also underway in Canada and the USA[90]. This will test the impact of reduction of fat intake to 20% of calories from fat and to increase the intake of fruit and vegetables in postmenopausal women aged 50 - 79. The trial discussed further in the section on diet below is sufficiently large to test the effects of vitamin D and calcium supplements on breast cancer incidence addressing the hypothesis that the variation in incidence between countries is in fact a north - south latitudinal trend associated with levels of solar radiation.

Dietary fat and the risk of Breast Cancer

The incidence of breast cancer varies about 6 fold throughout the world. International regression analysis of breast cancer incidence in relation to per capita fat intake suggests a potential for reducing the relative risk of breast cancer by around 24%[91]. The quality of data on national per capita fat consumption has however been repeatedly criticised. At least part of the apparent correlation may be due to a higher prevalence of reproductive risk factors or other environmental determinants in countries with a high fat consumption. The results of case control and cohort studies on the association between dietary fat and breast cancer are considered below.

Cohort Studies

A recent and assiduous review of cohort studies examining an association between dietary fat and breast cancer was undertaken by Willett[92]. Each study included at least 50 incident cases of breast cancer and quantitative estimates of fat intake as a proportion of total calories in the diet were available in six of the studies; the remaining analysed intake of fat from dietary records. None of the ten prospective cohort studies examined showed a significant association between fat and breast cancer comparing the highest category of fat intake with the lowest.

The average relative risk among studies which included a confidence interval (nine studies) was according to Willett 1.01 (95% CI 0.9-1.13). This covered a range from a relative risk of 0.62 in a 10 year follow up study with 99 incident cases identified out of a cohort of 5,485 to a relative risk estimate of 1.3 found in the Canadian breast screening cohort which identified 519 cases of breast cancer among a total cohort of 56,837 women[93]. Moreover restricting the analysis of studies to those concerned only with post menopausal women - since results from information regression analysis suggest that an association between fat and breast cancer may be stronger in older women - also failed to show a significant association. Relative risk estimates in these studies varied from 0.79 (95% CI 0.5-1.09) to 1.17 (95% CI 0.79-1.72)[94].

In reviewing the biases, which may affect the results of cohort studies, Willett concludes that none is sufficient to substantially alter his conclusion that there is no significant association between fat in the diet and the aetiology of breast cancer. It has been argued that non differential misclassification is responsible for effects that remain undetected in all epidemiological analysis[95]. This effect occurs where subjects are incorrectly assigned - in this case - either to high or low dietary fat categories. The effect is said to be non-differential where the magnitude of the error for one variable does not vary according to the actual value of other variables i.e. the fact of having breast cancer does not alter the direction of the bias. Non differential misclassification has the result of attenuating the rate difference towards its null value

thus reducing the likelihood of detecting a rate difference in incidence of breast cancer between subjects in high and low quintiles of fat intake.

Discussing in particular the Nurses Health Study, the largest prospective study including 89,494 women followed for eight years, Willett dismisses the importance of non differential misclassification of the data. Repeated assessment of dietary intake in cohort studies can alleviate the impact of non- differential misclassification yet is rarely reported in studies of dietary fat and breast cancer. All of the studies reviewed by Willett classified subjects and controls using a single estimate of diet. The Nurses Health Study did however include a validation exercise with detailed assessment of the diet of a sub group of 173 participants.

Willett suggested that correcting for measurement error using the increment of 24g/day for total fat intake which corresponded to the difference between the 10th and 90th percentile in relative risk assessment affected the relative risk only slightly from 1.01 (95% CI, 0.92 to 1.10) to 1.00 after de-attenuation. While Willett has uniquely among epidemiological analyses of this kind sought to improve precision caused by incorrect dietary classification, such an approach does not adequately account for inappropriate ascertainment of subjects in fat categories. This is particularly so where a time lag between exposure and effect may be important or when cumulative effects of diet are important. Willett does not discount the possibility that fat intake earlier in life or at substantially lower levels could influence the rate of breast cancer.

The Canadian Breast Screening Study,[96] although substantially smaller than the Nurses Health Study (total cohort size of 56,837 compared with 89,538) provides comparable quartile information for assessing the relationship between breast cancer incidence and dietary fat. The study by contrast to the Nurses Health Study concludes that there is a likely association between total fat intake and risk of breast cancer with a relative risk of 1.35 (95% CI 1-1.82) for 77g/day of fat. The association is shown to be independent of total caloric intake and not due to confounding by known breast cancer risk factors. This study was unable to distinguish unequivocally any difference

in effects from the major components of fat neither did it discern any increased effect for postmenopausal women.

The third relatively large cohort study to have analysed quantitative information in reviewing the relationship between fat and breast cancer is the National Health and Nutrition Examination Survey[93]. This study is substantially smaller than the two largest cohort studies discussed above having a total size of 5,485 women with 99 incident cases of breast cancer. The study showed no significant association between fat and breast cancer with the possibility of a negative association at low levels of fat intake. The study used a measurement method of 24-hour recall, which has been shown to be subject to considerable bias. The size of the survey is too small to distinguish effects for sub groups such as for different age of women or different components of fat in the diet.

Cohort studies while in general being more likely to demonstrate an effect than case control or ecological studies are nevertheless subject to substantial measurement error. Difficulties in assessing the dietary habits of individuals is well documented and is likely to give rise to considerable distortion and attenuation of relative risk. It can be argued that none of the instruments used in assessing diet can be properly validated since the time period over which diet may be most relevant to cancer risk remains unknown. Moreover the characteristics of individual cohort studies may have different potential for bias making a coherent review of results problematic.

In elucidating some of the effects of likely errors Howe[94] pointed out that the recall bias, which may occur if people with breast cancer interviewed after diagnosis of cancer report their diet differently to control subjects may be enhanced among groups such as nurses who are more likely to be aware of the postulated association between diet and disease risk. He highlighted two studies, which provide empirical information to support this view. Relative risks derived from a comparison of incidence of breast cancer in the highest to lowest quintile of fat intake in the Canadian National Breast Screening Study and the US Nurses Health Study were assessed from both retrospective and prospective dietary data. While there is no

evidence of recall bias in the Canadian study - the relative risks for total fat being 1.12 (0.76-1.66) and 1.05 (0.72-1.54) for retrospective and prospective data respectively there does appear to be an association between fat and breast cancer with a relative risk of 1.43 (0.9-2.27) based on retrospective data from the nurses study. This result is not confirmed by the prospective data which has a relative risk of 0.87.

Case Control Studies

A recent analysis of case control studies by Howe et al[97] show a significant association of increasing risk of breast cancer with increased fat intake in post - menopausal women which is unaffected after controlling for protein or carbohydrate intake or for non dietary variables. Relative risk was estimated per 45g/day of fat intake relating to consumption in a typical North American diet. Studies selected for inclusion in the analysis had all been completed by the end of 1986 and had used quantitative estimates of fat intake. From the 12 studies included - only 2 published during the relevant time period were excluded - there were 4,427 cases and 6,095 controls. Dietary information was assessed by food frequency data from the studies, estimates of standard portion sizes and nationally validated composition tables.

The strongest effect leading to an increased relative risk of 1.46 (95% CI=1.23,1.72;p<0.0001) for breast cancer was in postmenopausal women with an increased intake of saturated fat. The relative risk for monounsaturated fat was similar at 1.41 (1.19,1.67;p<0.0001). The relative risk for polyunsaturated fat was lower at 1.25 (0.9,1.71;p=0.16). In order to exclude the possibility that these findings were confounded by differences in the methodology or conduct of the studies, Howe et al undertook a restricted analysis of studies showing lack of heterogeneity. Intake of both total fat and saturated fat in postmenopausal women was associated with an increased risk of breast cancer with increased consumption and there was a statistically significant dose response relationship. These findings are unlikely to be due to chance. Howe et al argue that by removing inconsistencies between studies that may arise from differences in coding and techniques for analysis and by use of

original dietary records inconsistencies found in comparisons or reviews of case control studies have been removed.

Selection bias remains a substantial problem in case control studies. Non participation by controls or differential participation by controls following particular dietary practices cannot be excluded. Most of the cases in the Howe study were however population based and the refusal rate was low. Where the analysis was restricted to population controls excluding hospital controls there were little difference in the results.

An association between dietary fat and breast cancer ?

Epidemiological studies are inconsistent in their ability to detect a relationship between fat and risk of breast cancer. A number of authors have reviewed the strengths and limitations of studies including cohort, case, control and regression analysis but have continued to place different emphasis on the conflicting results.

In a "critical appraisal" of the evidence Goodwin and Boyd[98] set out a number of criteria for assessing the quality of the evidence based on the work of Bradford Hill[99]. They conclude that further investigation including the possibility of an intervention trial is needed to resolve the association. While a number of small studies show positive results the results from stronger designs are equivocal. Time trends and ecological studies are on the whole consistent with a positive relationship between fat consumption and breast cancer. These studies can however be criticised for lacking precision in measurements of true fat intake or make sufficient adjustment for the confounding effect of total energy intake.

In ecological studies the impact of dietary fat intake and risk of breast cancer are limited by the extent of variability of fat intake in the population (s) under review and the sensitivity of the measurement instrument for detecting true differences in dietary intake. If the heterogeneity of fat intake within populations is lower than that between countries, then the potential for detecting an association between fat and breast cancer

from national populations will be weaker than that found in international regression analysis and may be impossible to detect.

None of the studies undertaken by the main protagonists in the debate about a plausible link between fat in the diet and breast cancer can be insulated from these sources of error. Lack of heterogeneity e.g. may well affect the power of the nurses health study to show an effect. In seeking to resolve these conflicting results, Goodwin & Boyd estimated the difference in cancer incidence that might be found in association with fat intake within a country if the international data are indicative of a causal relationship.

Projecting onto a regression of breast cancer incidence and per capita fat consumption, the range in fat intake reported in the cohort study of Willet - from 44-32% of total calories - they concluded that this would be associated with only a small reduction in relative risk of cancer incidence of about 1.4. This estimate would be even smaller were it associated with other sources of measurement error. Using the validation study of Willet, Goodwin and Boyd[100] estimate the effect of misclassification on cancer risk associated with the highest and lowest quintiles of fat intake.

Comparing the numbers of women assigned to each quintile of fat intake according to their reported fat consumption from a semi quantitative dietary questionnaire or from diet records - an assumed gold standard more detailed record - and projecting relative risk from international regression analysis they estimated that misclassification could have reduced the apparent difference in risk in the nurses health study between the highest and lowest quintile from an expected 1.4 to only 1.16. This estimate is plausible in comparison with the relative risk found by Willet and is consistent with the more recent cohort study published by Howe.

By contrast for studies tending to show a positive association insufficient adjustment made for the impact of changes in overall energy intake when measuring fat in the diet and errors from selection bias and recall bias may reduce reported rate differences substantially.

Moreover, the relative risk of 1.46 in the review of case control studies was reported for a difference of 45g of saturated fat/day. The validity of such a reduction is questionable since many women may not be consuming such a large amount of fat to begin with[92]. Despite considerable variation in records of fat intake from international studies the average intake of fat in the Nurses Health Study was 25g/day. Willet points out that even women who consume in excess of 45g of fat/day cannot realistically reduce their intake by this amount because they cannot appreciably change their total energy intake. He argues that even a 10g reduction in saturated fat intake would be substantial. Using this incremental reduction instead of the 45g suggested in the Howe review would produce a relative risk reduction from 1.46 to around 1.1; recall bias may reduce this estimate still further.

Prentice and Sheppard[91] have sought to understand the discrepancy between observational epidemiological studies in order to shed some light on the change in breast cancer incidence which might be expected from a practical reduction in fat consumption. They argue that projected relative risk estimates from international regression analysis correspond well with observational studies given the limited variation in fat intake categories in even the best of most recent studies and acknowledging random errors in dietary assessment. While this is certainly reasonable in interpreting those case control studies which showed a significant positive association between daily grams of fat and breast cancer risk for postmenopausal women, the relative risks estimated from the North American nurses study are lower and of borderline significance only when sampling variation and measurement error are considered.

The results for premenopausal women are far less consistent. Indeed the trend for the nurses study appears to disagree with the international regression analysis. The cohort study published subsequently by Howe did however show a more consistent relationship between total energy adjusted fat consumption and breast cancer despite the first quintile being at increased relative risk to the second quartile. The results for

all women - both pre and post menopausal were 1.37,1.00,134 and 1.78 again broadly in line with error adjusted projections from international regression analysis.

Observational epidemiological studies have an effect of adding to, rather than clarifying the controversy surrounding an effect with such potential public health importance as a causal relationship between dietary fat and risk of breast cancer. There are 3 factors which, when combined, are likely to give rise to severe attenuation of any possible effect. These are the lack of heterogeneity in the studies, the potential for non-differential misclassification of data and other measurement errors associated with estimating diet.

This review of epidemiological evidence for the relationship between diet and breast cancer suggests that the better designed studies are able to control for family history or reproductive risk factors, but none of the studies has sufficient heterogeneity in fat intake to detect adequately the effect seen in international regression analysis.

An understanding of the biological plausibility of causal link between dietary fat and breast cancer cannot exclude the possible importance of diet at key development stages. In particular, the relationship with onset of menarche and early adolescence where the impact of diet on breast carcinogenesis may be profound. A number of studies have demonstrated a relationship between plasma oestradiol and other reproductive hormones with changes in fat intake[101,102]. This effect may be of major importance in determining age at onset of menarche and the pattern of ovulatory cycles setting the risk of breast carcinogenesis well before any potential mediation of effect with diet in adult life. The problems of a possible time lag between dietary intake and risk of breast cancer will also contribute to non-differential misclassification of subjects into fat categories, since early diet and adult diet may not coincide.

The error estimates made by Prentice & Sheppard, based on the validation study in the nurses cohort, arising from possible non differential misclassification of subjects was based on measurement of adult diet. Revising this still further to account for early

diet would severely undermine the potential of the study to show an effect. Other measurement errors discussed above would further contribute to the attenuation of any effect towards the null.

A number of authors have proposed a dietary fat intervention trial to tackle the controversy surrounding the possibility of a causal relationship between fat and breast cancer. The National Cancer Institute is now funding the Women's Health Initiative[103] designed to determine the efficacy of low fat diet in reducing the incidence of breast cancer, colorectal cancer and coronary heart disease in middle aged women. The study requires the recruitment of 32,000 women aged 45-69 and is underway in 20 centres in the USA. The trial is set to test the hypothesis with a statistical power of 80% that a 50% reduction in % of calories from fat (from 40% - 20% of total calories) will result in a detectable reduction in breast cancer incidence. The dietary intervention was tested in a feasibility study[90] and showed that dietary intervention can be achieved and sustained at relatively low cost. The women will need to be followed for 8.5 years to show an effect. While this approach will overcome many of the errors inherent in observational epidemiology it cannot fully address the question of aetiology of breast cancer because it only deals with adult diet.

Another possible approach is to consider a combined observational study across different countries which have substantial heterogeneity in dietary practice and which could stratify subjects according to their fat intake at different ages while still controlling for increased risk due to family history and reproductive factors. Such an approach using a pooled cohort or case control study would need to be of considerable time and long duration to demonstrate an effect. The feasibility may be enhanced by the increasing reliability and availability of cancer registries.

Deciding an appropriate public health strategy for primary prevention of breast cancer requires both an understanding of the aetiology of disease and the potential for modifying risk factors with specific interventions. A randomised controlled trial of suitable size and duration to assess the long term impact of dietary intervention, may elucidate the impact of reducing fat for women at different levels of risk.

A pooled epidemiological approach when corrected for both early diet and established risk factors would raise broader public health questions concerning the social determinants of diet during life phases where risk of breast carcinogenesis may be of greatest importance.

The only means of obtaining aetiologic information particularly where a plausible hypothesis includes a long time lag between onset of carcinogenesis and development of symptoms is through assiduous observational epidemiology. An appropriate study of the impact of diet on breast cancer would require a detailed review of diet for subgroups of women at substantially different levels of baseline risk. Detailed dietary assessment would be needed, based on repeated measures to validate the measurement instrument used and to reduce the potential for misclassification. Appropriate ages for dietary assessment would cover the timing of main life events where hormonal changes and the potential carcinogenesis would be greatest: onset of menarche, early adolescence and establishment of ovulatory cycles.

Conclusion

Summarising the evidence of benefits arising from alternative means of reducing mortality from breast cancer shows high and comparable estimates for relative risk reduction. The early Breast Cancer Triallists collaboration have provided convincing evidence for a 45-50% reduction in relative risk of death for women with early breast cancer taking tamoxifen therapy. The screening trials have proposed a relative risk reduction in mortality of around 24% - for screened women. The results from international regression analysis for the effect of dietary fat reduction on population mortality from breast cancer also suggest a possible 24% reduction with a low fat dietary intervention. Projections from adjuvant studies suggested a 30% reduction in mortality for tamoxifen chemoprophylaxis and results from the NSABP P-1 prevention trial increased this estimate to almost 50% based on reduction in incidence seen in the intervention group.

For an average district health authority population of 250,000 people with about 100 deaths from breast cancer per year full implementation of effective adjuvant therapy may prevent around 30-40 deaths, the screening programme may prevent 10-15 deaths. For preventive interventions the scope for dietary effects though far from proven may have the potential of saving 20-25 deaths; with tamoxifen chemoprophylaxis targeted only at say the 10% high risk women in the population would prevent only 5-10 deaths. These reductions in relative risk are of course tempered by the excess cost involved in each of the programmes, by the proportion of the population who may be affected and by the side effects involved. Screening for example has not yet been fully evaluated on a population basis but clearly has the limitation of being targeted only to a small proportion of the women at risk and potentially carrying a high cost per death prevented. The risks of both a high false positive and false negative rate further increase the costs involved.

The range of cost effectiveness discussed above for alternative means of reducing mortality from breast cancer are wide covering $17-50,000 (£10,625-£62,500) for early treatment of established disease to $40,000-160,000 (£25-100,000) in the breast screening programme. New and innovative treatments for advanced disease are of considerable cost for small benefit in terms of survival and assessments of quality of life for women on high dose chemotherapy are limited. Against this background the scope for chemoprevention is wide though ought to be targeted towards a cost effectiveness of less than £25,000 per death prevented.[34] This is a low estimate for the screening programme and a midpoint for effective treatment of breast cancer for women in the age group likely to be eligible for chemoprevention.

Chapter 2 sets out the rationale for chemoprevention of breast cancer with tamoxifen and addresses issues likely to impact on cost effectiveness. The issues are drawn from a literature review of the known adverse effects of tamoxifen as well as possible benefits associated with reduced risks of other conditions such as heart disease. Early discussion is included quantifying the risks and benefits for women who are taking long term tamoxifen despite being asymptomatic for breast cancer albeit at high risk for the disease. Information on the likely impact of long term use of tamoxifen on

morbidity is supported in subsequent chapters with empirical information measuring changes in the use of hospital services or use of prescribed medications by women taking tamoxifen or control within the International Breast Cancer Intervention Study. These are considered in Chapters 4 and 5 respectively.

Chapter Two

Breast Cancer Prevention with Tamoxifen: Prospects for Morbidity and Mortality

Introduction

This section is concerned with the rationale for chemoprevention of breast cancer and in particular the use of the drug tamoxifen for prophylaxis. Issues relating to chemoprevention of disease and the special nature of prevention trials are considered in the context of the likely risks and benefits of long term tamoxifen use and the trials currently underway in the USA, Europe and Australia. The side effects of tamoxifen are discussed in order to inform decisions about the costs of changes in rates of morbidity and mortality for high risk though asymptomatic women wishing to take prophylactic tamoxifen to reduce the risk of death from breast cancer. A balance sheet of risks and benefits is proposed as a basic design for the cost effectiveness study of tamoxifen chemoprophylaxis developed in later chapters. Issues of concern to the economic analysis are also discussed.

Chemoprevention can be defined broadly as the use of an anticancer substance - including pharmacological agents - to enhance intrinsic biological mechanisms that protect against the development of malignant cells. Such an intervention may be an appropriate action for individuals known to be at high risk for breast cancer or to have had precursor lesions identified through screening.[104,105] The rationale for chemoprevention of breast cancer, now under investigation in a number of countries is based on the assumption that therapeutic agents known to be active in suppressing tumour growth for women with early and advanced breast cancer are likely to be similarly effective in prevention. The expectation is that an agent effective in reducing the rate of development of disease for women with established breast cancer may be successful in correcting or inhibiting neoplastic agents responsible for the onset of carcinogenesis.

A number of authors reviewing the impact of adjuvant therapies on the development of breast cancer have suggested that the mode of action of the drug tamoxifen in reducing the development of recurrent disease in women with early breast cancer might apply also to preventing the onset of tumour development in healthy women[4,106,107,108]. Tamoxifen, a non-steroidal antioestrogen is used as the front line treatment for breast cancer. It is widely used in both pre and postmenopausal women as an adjuvant treatment in early disease where it has been shown to delay recurrence and increase survival and a recent review has provided convincing evidence of similar value for premenopausal women as adjuvant treatment[7].

There is little doubt that oestrogen is implicated in breast cancer carcinogenesis and although the precise mode of action of tamoxifen on the aetiology of breast cancer is complex it is clear that it blocks the tumour promoting properties of oestrogen[109]. Laboratory studies suggest that it is the amount of available oestrogen that is a key factor in the aetiology of breast cancer[110]. The amount of available oestrogen depends on levels of sex hormone binding globulin (SHBG) and other growth factors. Sakhai and other authors have reported that tamoxifen raised levels of SHBG[111,112,113].

Tamoxifen appears to have a range of effects acting as both an oestrogen agonist and an oestrogen antagonist. The effect appears to vary with menopausal status. It is more likely to behave as an antiestrogen in premenopausal women and as an oestrogen in postmenopausal women. Evidence suggests that tamoxifen is effective in oestrogen negative tumours though with a stronger effect in oestrogen dependant tumours[114]. Tamoxifen seems to be cytostatic rather than cytocidal in laboratory studies using animal analogues, supporting its use in prevention as well as in adjuvant therapy.

The impetus for testing tamoxifen prophylaxis in preventing breast cancer has been strengthened by concerns about the lack of progress made in reducing the burden of the disease despite advances in treatment and the development of breast cancer screening programmes. Moreover because of the high incidence of breast cancer even a small reduction in relative risk from a preventive intervention could considerably reduce morbidity and mortality and the high costs of surgical and medical therapies.

Estimates of the potential for tamoxifen prophylaxis of breast cancer on the burden of disease in the population have come from long term follow up in a number of adjuvant trials testing the effectiveness of tamoxifen in reducing the development of a second primary in the contralateral breast[114]. It is argued that this may be an effect equivalent to reducing the incidence of breast cancer in high risk women.

In the recent overview of trials of the use of adjuvant tamoxifen versus no adjuvant tamoxifen, the Early Breast Cancer Triallists Collaborative Group (EBCTCG) reported on 55 trials that began before 1990 and included almost 37,000 women. The overview divided trials into three categories of duration: one year, two years and more than two years; the latter being most usually five years or more. For these trials the proportional reductions in the incidence rate of contralateral breast cancer among women allocated tamoxifen were respectively 13% (SD 13), 26% (SD 9),and 47% (SD 9). The effect for one year was not significant but there was a significant trend (chi^2 =7.3,p,< 0.004) for trials of tamoxifen of two years or more with longer duration leading to greater reductions in the incidence of contralateral breast cancers. Overall the review shows that approximately five years of tamoxifen reduces the annual incidence rate of contralateral breast cancer by 50%[7].

It can be argued that this effect is equivalent to the prevention of breast cancer in healthy individuals since it is essentially suppressing the development of a second primary tumour[115]. It is possible however that the effect is to suppress the synchronous growth of tumours and that tamoxifen has no relevance in healthy women[116]. Moreover, these trials were concerned only with the development of breast cancer in postmenopausal women. Prevention is likely to be focused towards large numbers of healthy premenopausal women where the conditions for the development of tumours in women with risk factors for disease may be quite different.

The results from the EBCTCG overview of therapeutic interventions in breast cancer provides evidence that at least two years duration of tamoxifen can prevent recurrence and reduce mortality for women with early breast cancer by around 50%[7,110]. Were similar effects to be available for prevention particularly to women at high risk for

breast cancer the results could be of considerable public health significance since the incidence of breast cancer is high and the relatively long mean percentage survival relative to other cancers results in a prevalence :incidence ratio of about 10:1. Reducing the burden of disease in the population by around half could have considerable benefits for overall population mortality and result in substantial savings on the cost of health care.

Developing the concept of tamoxifen chemoprophylaxis within the broader context of a population based prevention trial does however raise a number of issues[118]. These include the likely costs and benefits of such an approach, the impact of the intervention on the burden of disease irrespective of the change in carcinogenesis found in individuals and the precise impact of deleterious side effects. Ethical support for a trial to test the hypothesis of chemoprevention in breast cancer would rely on the importance of identifying a group of women at relatively high risk for the disease in order to maximise benefit from a preventive intervention relative to possible harms involved[119].

Net benefits of chemoprevention would be gained at a cost both to the woman involved and in the resource use needed to set up a service for prevention. This includes the means of identifying high risk women, securing the compliance needed to make such a programme economically worthwhile, and providing adequate support and follow up. The prospect of routine screening for adverse events may also need to be considered. The net effect of chemoprevention can be summarised in the balance sheet below:

Cost of active chemoprevention
• the direct cost of the preventive intervention and associated treatment costs (drugs, staff, clinic facilities)
• the differences in costs of health services (including primary care and community health services) between those receiving the preventive intervention and control women (those at high risk receiving no intervention)

• activity: number of women eligible and taking up the preventive intervention (may include costs of identifying women at relatively high risk)
• the cost of "labelling" women at high risk creating anxiety
Benefits of chemoprevention will depend on
• the effectiveness of the intervention in reducing and delaying the development of the disease
• reducing or delaying the need for surgical or medical therapies
• improvements in quality of life
• the uptake of the preventive intervention
• beneficial effects on other organs
• impact on the health experience of women

How the allocation of aspects of chemoprevention set out in the box above is made could make a difference to the calculation of the ratio of costs to benefits and to the empirical results from the study developed in the analysis set out in Chapter 7. Consistency ofmethods in cost effectiveness analysis is clearly important also in the ability to make comparisons across health care programmes yet there appears to be little convention to guide the allcoationo f some of the a ttributes or indeed what attaributes shold be included. Some of the attributes listed as costs may arguably be considered benefits and vice versa. This is of particular concern for attributes such as changes in the quality of life or health experience of the women involved which are not always included in studies of cost effectiveness.

In general the use of resources on health care has been included in the numerator and the improvements in health in the denominator. The direct costs of the intervention – costs of service delivery including treatment costs are identified as costs as have the differences in use of health services between women receiving the intervention and those who are not. The uptake of the intervention – time spent by women seeking the intervention or indeed receiving it and the cost of targeting women are also ascribed as costs. These activities use resources and have no intrinsic health benefit to the women involved. The possible costs of labelling women at high risk and effects on

health experience such as those associated with changing levels of anxiety are also included as costs though perhaps should more properly be considered in the denominator since they are effects on health outcome. For this reason the possibility of benefits associated with potential improvements in quality of life arising directly from use of the intervention and the beneficial effects on other organs arising from the intervention are included in the denominator.

Less straightforward is measuring the costs or benefits associated with the effectiveness of the intervention and the impact on reducing or delaying the need for surgical or medical therapies. At this stage in our understanding of the potential for chemoprophylaxis of breast cancer it is difficult to know whether delayed onset of disease should be measured as changed resource use for health and personal costs of care – or as a health benefit. The problem arises because of possible changes in the morbidity experience of women with a raised risk profile for breast cancer. Neither do we know how the intervention may affect future risks or experience of life threatening illness and eventual cause of death. The attributes have been defined here as benefits based on the current evidence of changed health outcome from prevention trials particularly the NSABP P1 with 6 years of follow up.

The issue will be kept under review as new information emerges to further understand the impact of changes in intervention related morbidity in years that would have been lived anyway, costs that would have occurred in those years and health care costs – both related and unrelated to the intervention – that ensue in years that may be added – or lost as a result of the intervention. Future non-health related costs such as costs of living expenditure during possible additional years gained are not included. Studies from continued follow up of the women involved in IBIS will address the uncertainty in the allocation of costs and benefits and define more clearly how they might affect the calculation of costs effectiveness of tamoxifen chemoprophylaxis of breast cancer.

Chemoprevention - issues for both research and practice

The special nature of trials seeking to assess the efficacy of possible cancer prevention agents has been discussed by a number of authors[108,118]. Unlike treatment trials, prevention trials set out to recruit healthy individuals and usually need to be of long duration in order to monitor both the relatively rare event of the incidence of new cancers as well as assessing the progress of disease and the impact on mortality. In IBIS, for example, it is estimated that, for a power of 95% to show a significant difference of 40% between the two arms of the trial over ten years, 8,000 women are needed based on an average risk of breast cancer of 6 per 1,000 in the women recruited to the trial

Identifying a target group for breast cancer prevention trials has most usually rested on those at high risk for the condition under review. Trials for chemoprevention in breast cancer have sought to recruit women at high risk since the presence of risk factors was thought more likely to secure compliance and to reduce the expected trial duration and size because of the high expected incidence of new tumours[25,119]. In resolving the ethical questions concerning experimentation on healthy women it could be argued that recruiting women at high risk for a disease is more in line with treatment trials where the risk of mortality arising from the certain existence of a life limiting illness is balanced against the uncertain risks and benefits of the intervention under review.

Women age 50 at five or ten fold risk for breast cancer because of family history or reproductive factors have between a 30-50% remaining absolute lifetime risk of death from the disease. Women with elevated risk for breast cancer may find it acceptable to balance, in favour of trial entry, their higher than average lifetime risk of breast cancer with the possible reduction in risk or prolongation of disease free life years the agent under review and any likelihood of adverse events. Providing that the agent used in chemoprevention itself does not confer significant toxicity, trial entry for women with increased risk of breast cancer may be considered analogous to eligibility of women with established disease in treatment trials[118].

There are few medical alternatives available for women at high risk of breast cancer who seek active intervention in order to reduce their risk of early mortality from breast cancer. There is some evidence to suggest that either frequent mammography or prophylactic mastectomy may reduce the risk of mortality from breast cancer though precise information on these options is limited. Evidence of benefit from primary prevention as discussed earlier is scanty though studies are underway which may improve knowledge in this area[120].

There are, however, reasons why results obtained from studying women in high risk groups may not be generalisable to the general population. Evidence from studies of hereditary factors in the case of breast cancer suggests that women carrying the familial breast cancer gene, BRCA1 are more likely to have hormone independent tumours than women without this gene[9]. Tamoxifen used as an as adjuvant therapy for women with breast cancer is least effective with oestrogen negative tumours and may have little preventive impact on women likely to develop this kind of tumour[121]. Moreover the results from chemoprevention trials may be biased where power calculations for estimating trial numbers needed to show an effect are based on incidence of disease and not mortality[9]. Close monitoring of the population may result in detection of earlier stage disease and so reduce the perceived effect.

Side effects from long term use of tamoxifen

Large numbers of healthy asymptomatic women would need to take the preventive intervention in order to produce a significant impact on population mortality. Side effects found in adjuvant treated patients may be of greater concern in the context of prevention because of the importance of justifying the risk of possible harm from the intervention in relation to the benefits. Even rare side effects could lead to a large number of individual disease effects with considerable medical resource and social implications and any deleterious effects on common serious conditions such as coronary heart disease could outweigh the beneficial effects on breast cancer. It seems however that the balance of evidence suggests that a beneficial effect on lipid profiles which may reduce the risk of coronary heart disease in women taking tamoxifen is

more likely[122]. There may also be beneficial effects for the risk of osteoporosis although studies are few and equivocal[123,124]. Concerns remain about the long term metabolic impact of tamoxifen use particularly with regard to risks associated with endometrial cancer, thromboembolism and visual disturbance.

There is little evidence other than from the development of hyperplastic nodules and tumours in laboratory animals of an increased risk of liver cancer in women treated with tamoxifen though ascertainment of a primary tamoxifen induced liver cancer may be difficult in adjuvant studies[125]. Liver cancer is a rare condition and it is now generally agreed that any diagnosis of liver cancer in women taking tamoxifen is most likely to be due to metastatic spread of the disease. Cuzick reports that the available evidence from trials has failed to show an effect on liver cancer and a large scale epidemiological cancer registry based study in the United States found no sign of any increase in liver cancer after the introduction of tamoxifen in 1977[126]. In the EBCTCG there were slightly fewer deaths attributable to liver disease in the tamoxifen treated group than in the control group and there was no excess of liver cancers in the tamoxifen group even among Japanese women where the incidence of liver cancer is relatively high (no liver cancers in the tamoxifen group versus three in the control group).

Ocular toxicity from long term tamoxifen treatment is uncommon though case reports and case series report clinical changes such as retinal deposits, macular oedema and corneal thickening. A review of tamoxifen related eye disease documented considerable variability in the presentation of these conditions which may be due to alternative explanations such as age related eye disease or ocular changes caused by other diagnosis such as diabetes. There does however seem to be an increase in severity of ocular findings and more serious visual impairment in patients with advanced breast cancer on high dose adjuvant therapy including tamoxifen. Prospective data from a review of randomised controlled clinical trials suggests that ocular complaints may be more frequent among patients taking chemotherapy but that there is little difference in symptoms for women on tamoxifen alone compared with control. Since there is, at present, no clear evidence that long term tamoxifen use

predisposes to ocular degeneration there is little justification for routine eye tests prior to treatment. Nevertheless some authors have suggested that close monitoring might be advised [127,128,129].

Evidence from published studies concerned with the side effects from tamoxifen that are most likely to influence the beneficial effects of tamoxifen in chemoprevention of breast cancer is reviewed below. This includes general symptoms, endometrial cancer, thrombolic events such as deep vein thrombosis (DVT) and pulmonary embolism (PE) and effects on lipid profiles and cardiac health. Where possible the information has been summarised to identify a rate which could inform assumptions about the 'cost' of side effects and the impact they may have on uptake of a preventive intervention and long term compliance with the treatment regimen.

General symptoms

Reporting of rates of symptomatic side effects is inconsistent though numerous case reports and observational studies document a change in endometrial epithelia with the appearance of polyps in tamoxifen treated women and frequent increase in gynaecological symptoms such as irregular menstruation, hot flushes and vaginal discharge[8,130]. Some of the reported side effects such as hot flushes are clearly associated with anti-oestrogenic properties of tamoxifen whereas vaginal discharge or bleeding may be associated with its oestrogenic properties[131].

Many authors concerned with the survival value of adjuvant tamoxifen refer to the relatively infrequent reporting of symptomatic side effects by women taking tamoxifen in comparison with control patients[132]. A six year follow up of women treated with tamoxifen as a single agent following surgery, for example, found that only 4% of patients treated with tamoxifen for two years had side effects requiring withdrawal from the trial[133]. Yet, many long-term studies do report an increase in side effects for women on tamoxifen. A large scale NSABBP[134] study of over 3,000 women with oestrogen receptor positive cancers randomised to receive either tamoxifen (n=1422) or placebo (n=1439) found that the frequency of occurrence of

many symptoms such as fluid retention and nausea was similar in the two groups. Symptoms such as hot flushes and vaginal discharge were however higher in the tamoxifen treated group and did cause women to withdraw from the study though the rate of withdrawal was not documented.

Love specifically reported on symptoms associated with tamoxifen in a group of 140 volunteer post menopausal women in the context of a blinded randomised trial[121]. They were assessed over 24 months. All of the women had axillary node negative breast cancer in remission. He found a significant level of side effects for those on tamoxifen compared with women on placebo. The study participants were comparable for mean age, years since menopause, body mass and prior hysterectomy and had comparable levels of the symptoms under review at the beginning of the study. None had active radiological, laboratory or clinically verifiable breast cancer at the time of the study.

After the first 12 months of the study 61.7% (31/64) of women taking tamoxifen reported hot flushes compared with 48.4% (37/60) on placebo. The significant difference in rates appeared at the six month visit and was sustained over the study period. Fewer women overall reported severe hot flushes in the first six months though there was a significant increase for women taking tamoxifen. 13.3% (8/60) of women taking tamoxifen reported severe hot flushes compared with 3.1% (2/64) in the placebo group. Reporting of hot flushes of any kind were equivalent at baseline. Rates of moderate to severe face flushes also increased significantly for the tamoxifen group after the first three months. Powles found a similar result of a two fold increase in the occurrence of hot flushes in tamoxifen treated women though this effect was mostly confined to premenopausal women.

A significant increase in general gynaecologic symptoms was also reported in this study. By 12 months of follow up, 26.7% of women in the tamoxifen arm reported gynaecological symptoms compared with 14.1% at baseline. Gynaecological symptoms also increased in the placebo arm though to a much lesser extent not reaching significance over baseline values. The women in the tamoxifen arm had a

higher proportion of gynaecological symptoms at baseline than the women in the placebo group though this difference was not significant. In the Powles pilot women also reported a significant increase in vaginal discharge and in menstrual irregularities. The Love study found no differences in a number of symptom areas such as in joint pain, fatigue and nausea though there was an apparent reduction in the rate of reports of headache in the tamoxifen group. The Powles study showed a reduction in reporting of nausea and vomiting in tamoxifen treated women though no difference in headaches between the two groups.

In the Love study, the apparent delay in the appearance of side effects for some women and the fluctuation in reporting over time led the investigators to identify a category of persistent side effects. Women taking tamoxifen showed a higher level of overall toxicity with persistent side effects reported by 48.5% (16/60) at 12 months compared with 21.2% (14/66) in the placebo group. Undertaking an assessment of well being using a seven item quality of life measure the authors also found that women who experience symptoms are more likely to report anxiety about involvement in the trial. They conclude that a protocol should be devised for proper evaluation and management of the side effects and that the decrement in quality of life to women on tamoxifen be more fully documented

Endometrial Cancer

An excess of endometrial carcinoma has been identified from a number of studies of long-term follow up of women on adjuvant tamoxifen and more recently from the results of the NSABP P-1[2]. These studies suggest that the effect may be related to the dose of tamoxifen used and the duration of use. The NSABP B14 trial of tamoxifen adjuvant therapy in women with breast cancer has now accumulated 18 cases of endometrial cancer out of 2,638 patients with no cases reported in the control group[134]. This includes seven patients allocated to the tamoxifen group after the initial phase of randomisation and two patients who relapsed in the placebo group and were subsequently assigned to tamoxifen. The median time to development of endometrial cancer in the 11 randomised cases was 41 months (range 4-93 months)

In the Stockholm Adjuvant Tamoxifen Trial 13 out of 931 women (1.4%) taking tamoxifen developed uterine cancers compared with two out of 915 women (0.2%)in the control group. The stage of these tumours was not uniform[135]. Both early and late stage grades were found challenging previous assumptions that tamoxifen induced cancers may be of lower grade and have a more favourable prognosis than those found in patients not taking tamoxifen[136].

Dose is clearly an important factor in this trial since the women were taking tamoxifen at 40 mg/day which is twice that offered in most adjuvant studies or in prevention trials. It has been estimated that the median cumulative dose of tamoxifen needed before increased risk of endometrial cancer is around 29g. This level would be reached after four years of treatment with a daily intake of 20mg. Duration of treatment was also important in this study with the number of cases of endometrial cancer increasing in those treated for longer than two years[137].

The Scottish Adjuvant Study[138] by contrast, found no association between endometrial cancer and tamoxifen therapy at a dose of 20mg/day in 4-10 years of follow up of 1,070 randomly allocated postmenopausal women. The Danish Adjuvant study [139] also failed to show a statistically significant increase in endometrial cancer in women taking tamoxifen alone at a dose of 30mg/day or with radiotherapy although there was a non significant trend towards an elevated risk in the tamoxifen treated group. A similar result of a non significant increase of uterine cancer for women on tamoxifen was shown in the South Sweden study with 719 breast cancer patients randomised to either radiotherapy with tamoxifen, radiotherapy alone or tamoxifen alone, after nine years of follow up[140]. The NATO study[133] of 20mg daily of tamoxifen given to postmenopausal women with early breast cancer also found no endometrial cancer after two years of follow up.

A recent report pooling the results of randomised studies on the impact of tamoxifen on endometrial cancer suggests that there is a statistically significant increase in relative risk of about 4.8 in the rate of development of endometrial cancer in women

with breast cancer treated with tamoxifen compared with women in the control group. For women receiving adjuvant tamoxifen at a dose of 20mg per day the relative risk appears to be about 4.08.

The results from NSABP P-1[2] show an increased relative risk of endometrial cancer of 2.53 based on the appearance of 33 cancers in the tamoxifen treated group (out of 6,681) compared with 14 (out of 6,707)in the control group. The increased risk was predominantly in women aged 50 or older with an increased relative risk of 4.01 (95% CI=1.7-10.9) compared with a relative risk of 1.21 in women aged 49 or younger (95%CI= 0.41-3.60). The appearance of endometrial cancer occurred early in the follow up period and had an average annual incidence of 2.3 per 1000 in the tamoxifen group compared with 0.91 in the control group. The cumulative incidence was 13 per 1000 women in the tamoxifen group at 66 months of follow up compared with 5.4 per 1000 in the control group. The estimate is lower than might be expected from adjuvant studies though a large proportion of the women in the trial had undergone hysterectomy. The increased relative risk found in adjuvant studies is similar to that seen in the Royal Marsden Chemoprevention pilot. In this study there were four endometrial cancers reported after 70 months of follow up out of 1238 women on tamoxifen compared with one woman with endometrial cancer out of 1233 analysed on placebo.

Thromboembolic effects

There is evidence of an increased risk of thromboembolic events in women taking tamoxifen though this mostly comes from case reports and large adjuvant studies of women with established breast cancer where the causes of changes in haemostasis may be complex and multifactorial. There is considerable evidence of both an association between cancer in general and risk of thromboembolism and of risks caused by cancer chemotherapy. It is difficult to isolate the likely increased rate of thromboembolism which can be attributed to tamoxifen from these studies because they compare a variety of different chemotherapeutic regimen vs. Tamoxifen. Few studies are available to isolate the impact of tamoxifen in comparison with placebo.

The regimen are inconsistent both in the dose and duration of tamoxifen and in the age, menopausal and cancer status of the women involved. Most of these studies arise as a secondary analysis in a design primarily seeking to assess the effect of tamoxifen on recurrence rate and survival rather than to identify the precise rates of likely thromboembolic complications. They may not have sufficient power or length of follow up to address questions of toxicity. The studies vary in the extent to which they record thromboembolic complications in particular at what level of severity symptoms are included. Not all studies for example include thrombophlebitis. Table 1 summarises the rate of thromboembolic complications for women taking tamoxifen.

Table 1: Summary of risks of Thromboembolic disease in randomised adjuvant studies (20mg tamoxifen daily)

Study	type	n	follow up	event rate	note
Fisher [132] women<70 primary breast cancer, node negative estrogen +	adjuvant tamoxifen , double blind, placebo controlled	2644 analysed 1326 on placebo;1318 on tamoxifen(but 141 loss to f/u)	4years follow up	Event rate 0.9% in tamoxifen group,0.2% in placebo group.	designed to study the recurrence and survival benefit of tamoxifen

Saphner [140]	A review of 7 adjuvant studies (USA)	2673 patients in total chemotherapy vs. chemotherapy w tamoxifen observation, chemo or chemo w tam tamoxifen vs. placebo chemotherapy vs. observation chemotherapy w tamoxifen followed by radiation vs. observation chemotherapy w tamoxifen followed by observation or chemotherapy with tamoxifen followed by tamoxifen chemotherapy w tamoxifen vs. chemotherapy w tam	3-5 years follow up	frequency of venous complications in comparisons including *tamoxifen* vary from 2.3-9.1% compared with 0.4% for observation and between 3.5 and 3.8% for chemotherapy in postmenopausal women. For premenopausal women range is 1.4-4.2% compared with less than 1.4%for chemotherapy alone and no findings for women under observation alone	seeking estimates of the frequency of venous and arterial thrombo-embolism and the contribution of chemotherapy with tamoxifen by reviewing studies of combination therapies and including patients on observation alone
Fornander [142] Stockholm Adjuvant Tamoxifen Trial	Data on intercurrent morbidity (hospital admission) and mortality from an rct of adjuvant tamoxifen vs. no endocrine therapy	1846 patients; 931 tamoxifen, 915 control with further randomisation by risk status to radiation and chemotherapy	2 years with further 3 years re randomisation	The frequency of admissions for thrombotic events was 2% in both the tamoxifen and control group	adjuvant study
Pritchard & Paterson, [143]	rct of *tamoxifen* for 2 years vs. *tamoxifen* and chemo (6 *months*)	352 women receiving tam alone; 353 receiving tam plus chemo	2 years	combination therapy led to 13.6% thromboembolic events (with significantly more serious grades including 3 deaths) compared with 2.6% in women randomised to tam alone	
Breast Cancer Prevention Trial [2]	rct of tamoxifen vs. placebo for women at high risk of breast cancer	13,388 women randomised to either tamoxifen (6681) or placebo (6707)	median follow up is 3.5 years	women taking tamoxifen 1.5% thromboembolic disease: pe (.25%), dvt(.45%,cva (.5%)	the absolute risk difference between the tamoxifen and placebo arm is less than 5 per 1000 women for all events (less than 2 events per 1000 women for pe alone)

Only randomised studies of adjuvant therapy which are able to measure the incidence of thromboembolic events prospectively and account for possible confounding factors such as the age and menopausal status of the women involved are included.

The study by Fisher et al compares the incidence of thromboembolic events in a double blind placebo controlled trial. The rates of thromboembolic events reported in this study are small compared with other studies though it was the clinically most important side effect occurring in 0.9% of patients receiving tamoxifen compared with

0.2% in the placebo group; a relative risk for women taking tamoxifen of 4.5. The excess was however mostly accounted for by thrombophlebitis and few details are given about the specific conditions involved or the grade and severity of the complications experienced.

Thromboembolic complications were significantly more frequent among patients receiving adjuvant therapy than those 'observed only' following surgery in a review paper summarising results from seven consecutive adjuvant studies by Saphner et al for the Eastern Co-operative Oncology Group[141]. The paper seeks to subdivide and group the studies in order to make conclusions about the impact of both hormonal and chemotherapeutic treatment alone or in combination on the development of arterial or venous complications in both pre and post menopausal women.

Arterial thrombosis occurred in the same frequency in both pre and postmenopausal women. Premenopausal patients receiving chemotherapy and tamoxifen developed significantly more venous thrombi than patients who received chemotherapy without tamoxifen. Premenopausal patients only developed arterial thrombosis when on this combined regime. Likewise among post menopausal patients the combination of tamoxifen and chemotherapy was associated with a significantly higher frequency of venous thrombosis than tamoxifen alone. Postmenopausal patients receiving regimen with tamoxifen alone or in combination with chemotherapy did not experience different levels of arterial thrombosis in comparison with patients on observation only.

The study lacked patients in sufficient numbers with consistent regimen to fully assess the impact of tamoxifen alone although the tamoxifen placebo controlled trial included in the review suggests a rate for post menopausal women of 1.2% for arterial events and 2.3% for venous events. Post menopausal women taking placebo in this study did however experience a very high rate of arterial events (4.8%) by comparison. Tamoxifen appears in this review to be associated with only a marginally increased risk of thrombosis. The rate of arterial events did not exceed 2.9% in any of the studies which included tamoxifen. Venous events ranged from 1.4% to 10.4% though these were all in combination with chemotherapy.

No significant toxic effects were evident in a study reported by Fornander et al of hospital admissions of women involved in the Stockholm Adjuvant Tamoxifen Trial though the median follow up was only 4.5 years and the data are limited in detecting complications that do not result in a hospital visit. Thromboembolic events were reported in 2% of cases in both the tamoxifen and the placebo arm.

The study by Pritchard and Paterson supports the finding emerging from the review study described above that the major risk of thromboembolism for women with breast cancer occurs primarily with combination therapy. In a randomised trial of tamoxifen vs. combination therapy the authors report a strikingly high incidence of thromboembolic events of 13.6% among women randomised to receive chemotherapy with tamoxifen while only 2.6% of women in the tamoxifen arm experienced thromboembolism of any sort. Most of the complications including a number of severe effects and 3 fatalities occurred during chemotherapy. The authors conclude that the relatively common and serious impact of thromboembolism in this trial may preclude the routine use of combination therapy for women with breast cancer. Thromboembolism resulted in 26 hospitalisations in the combination arm and only three in the tamoxifen arm. A broad definition of thrombotic events was however used in this study and superficial phlebitis was included. The trial used 30mg/day of tamoxifen which is a high dose compared with that used in most other adjuvant studies and in prevention trials.

The Early Breast Cancer Triallists Collaboration have recently presented an updated overview of randomised trials of adjuvant tamoxifen which increases substantially the amount of information available on long term use[7]. The review reported one extra death due to thromboembolism per 5,000 woman years of tamoxifen use though this excess was not statistically significant. No thrombolic events were reported for women under 50, women over 70 or for those taking tamoxifen for five years of treatment or more. No information was collected on non fatal thromboembolic effects.

In NSABP P-1 there was a significantly increased risk of pulmonary embolism for women taking prophylactic tamoxifen. Women randomised to the tamoxifen group experienced a greater number of both pulmonary embolism (18 in the tamoxifen group compared with six in the placebo group) and deep vein thrombosis (35 versus 22 cases) compared with women in the placebo arm. This included two episodes of fatal pulmonary embolism in women randomised to taking tamoxifen. This excess risk occurred primarily in women aged 50 and over. The increased relative risk of pulmonary embolism was almost three fold for women on tamoxifen though the absolute risk difference for all thromboembolic disease reported in the study between the control and intervention arm is less than 5 per 1000 women. This includes both stroke (34 cases for women on tamoxifen and 24 in the control arm) and transient ischaemic attack (TIA) (18 for women on tamoxifen and 21 for women in the control arm) with 99 events in total for women on tamoxifen compared with 70 in the placebo group.

The overall relative risk of thromboembolic disease was less than two for women on tamoxifen compared with women on control. The result is similar taking deep vein thrombosis and pulmonary embolism together excluding cerebrovascular disease and when the incidence of stroke and TIA is included. A similar result was found in findings from the Royal Marsden study [144] with a relatively low incidence of thromboembolic events but an increased relative risk of 1.7 for deep vein thrombosis and pulmonary embolism in the tamoxifen arm compared with women on placebo.

A number of studies have sought to assess the biochemical effects of tamoxifen on the haemostatic system. Decreases in antithrombin III - which inhibits thrombin and other activated clotting factors have been reported in patients treated with tamoxifen for advanced disease [145] or as an adjuvant therapy in node positive breast cancer although these have not been recorded to the levels which might be expected to increase the frequency of blood clotting. Manucci et al in the Italian prevention study [146] published results of heamostasis and lipid measurements on the first 68 consecutive women enrolled in the study at one, two, three and six months after entry. Tamoxifen induced a modest non significant decrease in anticoagulant proteins though there were

no signs of activation of fibrinolysis or protein markers of coagulation. Other studies have also demonstrated a decrease in levels of antithrombin III though few have found changes which would appear to have clinical significance.

Jones and Powles[147] found no increase in fibrinogen levels which would be associated with an increased risk of thromboembolism in healthy women participating in the randomised double blind prevention trial underway at the Royal Marsden up to 36 months after recruitment though any history of venous thrombosis or pulmonary embolism are significant exclusion criteria for the trial. In fact for both pre and post menopausal women there was a sustained, significant reduction in fibrinogen levels over the first year of follow up. There was no reduction in antithrombin III for premenopausal women and only a small reduction (less than 10%) in postmenopausal women. In the absence of positive results with fibrinogen and antithrombin III the authors measured other molecular derivatives involved in blood coagulation, principally Protein C and Protein S. Inherited deficiency in these proteins is associated with an increased incidence of deep vein thrombosis.

The study found a marginal reduction in Protein S at six months though not at clinically significant levels and no change in Protein C. The authors speculate that the increased risk of thrombotic events associated with tamoxifen use may be due to an inherited tendency in patients at risk of breast cancer or with diagnosed disease[145,148].

The increased risk for women taking tamoxifen as adjuvant therapy may be considered acceptable because it is outweighed by the beneficial effect of tamoxifen on disease free survival. Further research is needed to establish whether prior screening for congenital clotting disorders is likely to be feasible and effective for women seeking tamoxifen prophylaxis, especially given the low incidence. In any event eligibility criteria should continue to exclude women with previous history of thromboembolic disease.

By contrast there is convincing evidence for a beneficial effect of tamoxifen on risk factors associated with cardiac health. In general, studies conclude that the favourable

impact of tamoxifen on lipid profiles is likely to translate into reduced risk of both death from coronary heart disease and cardiac morbidity requiring hospitalisation or long term drug treatment[149,150]. This relationship has however been more thoroughly investigated in men than in women. Clinical reports and case studies suggest that the change in lipid profiles for women taking tamoxifen may be mediated by the drug's oestrogenic effect producing a reduction in total serum cholesterol principally due to a lowering of low density lipoprotein. Follow up of patients mostly in studies of adjuvant tamoxifen for women with breast cancer suggest that the reduction in mean total serum cholesterol might be around 12% with a lowering of LDL cholesterol of 20%[151]. Such an effect if sustained could lead to an anticipated reduction in risk of coronary heart disease which might be as much as 20%[152].

Lipids

In a double blind randomised trial of 140 postmenopausal women who were disease free after primary treatment for node negative breast cancer, Love[150] reported a significant decrease of 12% in total cholesterol, largely due to a 16% reduction in LDL cholesterol at three, six and 12 months of follow up. There was a also a small but significant reduction in HDL cholesterol which might be expected with a reduction in total cholesterol. Powles et al[119] in early reports from the UK chemoprevention pilot found significant reductions of around 15% in total cholesterol and reductions in LDL cholesterol in both pre and post menopausal women after two years of follow up. These findings were confirmed in further follow up[144] with a total of 400 women with the addition of a significant reduction in apolipoprotein B in postmenopausal women. There was no effect on HDL cholesterol. A subgroup analysis from this study[152] found a 13% reduction in total cholesterol in a small group of women who were also taking hormone replacement therapy.

Studies of the impact of lipid lowering on coronary heart disease suggest that the effect is related to both the extent of lipid lowering and the duration of the effect. The effect appears to increase with duration of taking tamoxifen although published reports from such sub group analysis is limited[153,154].

Few studies are available however to quantify the impact of tamoxifen on death from coronary heart disease or on cardiac morbidity. In the first report from the Early Breast Cancer Triallists Collaboration overview of adjuvant trials tamoxifen was associated with reductions of 25% (SD13. 2p=0.06) in deaths from vascular causes[24]. Results from the more recent longer term follow up of these randomised trials[7] were consistent with these findings though the difference for vascular causes was not significant. There was no significant difference in deaths from myocardial infarction between the two arms of the trial. Likewise tamoxifen administration did not alter the average annual rate of ischaemic heart disease in the NSABP P-1[2]. The number of women who had a myocardial infarction was 28 in the placebo group and 31 in the tamoxifen group. There was no significant difference in fatality between the placebo and tamoxifen group with 7 and 8 deaths respectively. There was also no significant difference in reporting of cardiac morbidity between the two groups including angina and acute ischaemic syndrome.

A significant reduction ($p<0.005$) in the incidence of fatal myocardial infarction was also demonstrated in the Scottish Adjuvant Tamoxifen Trial although there was no significant difference in the incidence of other fatal vascular events in the two arms of the trial[155]. Of 200 deaths in the tamoxifen arm (n=539) ten were due to myocardial infarction compared with 25 out of 251 deaths in the control arm (n=531) of the trial. This 38% reduction in relative risk of death from myocardial infarction was measured after a mean duration of 29 months (9-93) with tamoxifen taken at a dose of 20 mg daily. The results may underestimate the effect since the non intervention arm of the study included some women who crossed over to taking tamoxifen on relapse.

Further follow up of this trial population using record linkage with the inpatient record scheme at the Scottish Home and Health Department found statistically significant differences between the rate of admission to hospital for women taking tamoxifen and those in the control arm of the trial with a hazard ratio 2.03 (1.05 - 3.92, p=0.033) for myocardial infarction. The effect was greatest in current users of tamoxifen suggesting that the protective effect may diminish once treatment stops[156].

These results are consistent with studies showing that the reduction in serum cholesterol and LDL cholesterol is greatest in current users than in former and non users of tamoxifen[154]. Some non significant reduction in the incidence of other cardiac ischaemic episodes was also seen in this study.

A significant reduction in overall cardiac morbidity in women taking a daily 40mg dose of tamoxifen as adjuvant therapy was shown by the Stockholm Breast Cancer Study Group[151]. The confidence intervals are too wide to offer a convincing effect for specific cardiac causes; there is a significant reduction in relative hazard of admissions for MI (0.68 0.48-0.97) and a trend towards reduction for angina pectoris as well as other forms of ischaemic heart disease such as congestive heart failure and myocardial ischaemia. This study did however show a statistically significant benefit in terms of cardiac morbidity for longer duration of treatment with patients treated for five rather than two years. There was a significant decrease of admissions due to any cardiac disease in the five year group (relative hazard, 0.37, 0.15-0.92 p=0.03). The authors conclude that longer follow up is needed to determine whether this benefit will be translated into a significant reduction in cardiac mortality.

In the context of chemoprevention of breast cancer for women at high risk the impact of tamoxifen on mortality from coronary heart disease may be at least as important as the reduction in risk from breast cancer[152,155]. Among women at high risk for breast cancer the probability of death from breast cancer relative to death from other causes decreases with time; mortality from coronary heart disease particularly ischaemic heart disease becomes of far greater significance.

Bones

Because of its oestrogenic properties it is assumed that tamoxifen may have a beneficial effect on the rate of bone loss in post menopausal women. Studies in postmenopausal women taking tamoxifen have found positive changes in bone activity markers and in general a significant increase in bone mineral density (BMD). The clinical significance of these changes in terms of reduced fracture risk or

mortality is less clear though, it is unlikely from present evidence that the effect will be deleterious. The NSABP P-1 recorded fracture rate and reported a significant reduction in hip fractures for women taking prophylactic tamoxifen. The effects of tamoxifen on premenopausal women is more difficult to discern because the numbers of younger women included in studies is small. Some authors have expressed concern that tamoxifen may antagonise oestrogen in premenopausal women leading to bone loss[159].

A number of adjuvant studies have included an assessment of the impact of tamoxifen treatment on bone mineral density. In general, even where studies have been unable to demonstrate a reduction in the rate of bone loss in postmenopausal women the effect has been one of no difference in comparison with women in control groups rather than of an acceleration in bone loss[160,161,162]. A study of the interaction between HRT use and tamoxifen use also concluded that there were no adverse effects in postmenopausal women.[152].

Larger and better controlled studies have on the whole shown an increase in bone mineral density in postmenopausal women taking tamoxifen of the order of 1.5% per year compared with - as expected - a loss of bone mineral density in control groups. In a randomised study of 140 postmenopausal women with breast cancer taking either 20mg daily of tamoxifen or placebo, Love et al found strong evidence for a significant reduction in the rate of bone loss in the lumbar spine in tamoxifen treated women[163]. There was no similar effect in comparison with the placebo group on radial bone; bone mineral density in both the tamoxifen and placebo group declined over the two years of measurement. Assessments of bone mineral density in the femur were not made and there was no assessment of the impact on long term fracture rate. The authors conclude that tamoxifen is an anti - resorptive agent affecting those bone sites normally affected by oestrogen. The 3% increase - in bone mineral density, over the two year follow up, found in this study - even after correcting for menopausal status at the time of diagnosis of breast cancer in the lumbar spine, is within the range seen with agents commonly prescribed for oestrogen replacement therapy.

Results from a 40 month follow up of women enrolled in the Marsden tamoxifen prophylaxis pilot found no effect on bone mineral density in the forearm for women in the tamoxifen arm of the study even where postmenopausal women only were considered[144]. Results of BMD in the lumbar spine and hip did however show an effect of tamoxifen and are discussed below. The same effect from forearm measurement was found in 75 women enrolled in the Swedish tamoxifen trial after either two or five year follow up[164]. Forearm measurement of bone mineral density showed no significant differences for women randomised to tamoxifen in the treatment arm compared with control even at the high dose of 40mg daily.

Evidence on the longer term impact of tamoxifen is available from a five year assessment of 62 of the original subjects by Love et al[165]. This study confirmed the increase in bone mineral density in post menopausal women taking tamoxifen though with no significant further increase from the two year level. Further assessment of longer term effects are reported by Cuzick and Baum[142] reviewing a wide range of biological markers including measures of bone mineral density in the spine and trochanter of both current and ex - users of tamoxifen. 73 ex - users were compared with 60 controls; the median follow up was seven years. Bone mineral density was about 11% higher among current users compared with both ex - users and controls and the effect was greater in postmenopausal women. None of the differences achieved significance though the consistent difference between current users compared with both ex - users and control suggests that the effect of tamoxifen may be lost with cessation of use. Measurements were not made on 21 of the women in this study and the number of premenopausal women included was too small for subgroup analysis.

Significant results were found in an analysis of bone mineral density made in the lumbar spine and femur over three years for women enrolled in the Royal Marsden Prevention pilot as discussed earlier[144]. In premenopausal women, BMD in the lumbar spine decreased progressively and was significantly lower than pre-treatment values at year one (n=49), year two (n=32) and year three (n=19). Overall, there was a loss of BMD in the lumbar spine of 1.44% per year for women in the tamoxifen group compared with a small gain of 0.24% per year for premenopausal women on placebo.

At the hip there was a significant loss of BMD in premenopausal women in the tamoxifen group compared with baseline values by the third year and compared with the placebo group by the second and third years. For postmenopausal women taking tamoxifen compared with placebo there was a significant increase in BMD at both the hip (average annual increase of 1.71%) and the lumbar spine (average annual increase of 1.17%) mostly occurring in the first year of treatment. Larger studies are needed to confirm the results for premenopausal women. For postmenopausal women taking tamoxifen there appears to be a consistent effect increasing bone mineral density by an annual average of 1.5% though the long term duration of this effect and its clinical significance are not properly understood.

Quantifying risks and benefits of chemoprophylaxis

Few authors have been able to quantify the health benefits and costs of chemoprevention for breast cancer in terms of life expectancy or in terms of costs in relation to life years gained because of the lack of information on efficacy or costing from randomised controlled trials or observational studies. Broad theoretical estimates derived from the rationale for the NSABP P-1 trial have been attempted by Nease and Ross[12]. Based on a 50 year old woman with a breast cancer risk twice that of the average woman her age they argue that prophylaxis with tamoxifen offers an increase in life expectancy of about nine days. This estimate is based on decision analysis which accounts for increased relative risks of non fatal endometrial cancer and of death from thromboembolism of 2.4 and 3.5 respectively - and beneficial effects on risk of death from myocardial infarction and hip fracture of 0.2 and 0.25. Risk of mortality from breast cancer is estimated to reduce by 35%. These results are in line with findings from Cuzick[126] who estimated a slightly higher result of 40% reduction in breast cancer incidence, the same level as for ischaemic heart disease risk with slightly greater benefits on bone (reduction of spinal fractures by 33%) with a lower adverse effect on thromboembolic disease (approximately two fold increase).

Such a modest net improvement in health is clearly dependant on the estimates used for comparative relative risks between detrimental and beneficial effects and widely

differing conclusions arise from relatively small changes in the assumptions. No account is taken in this model of changes in quality of life or other non life threatening conditions or of the weight to be attached to changes in risk of death from different causes. The changes discussed in this study include changes in mortality from myocardial infarction, thromboembolic causes, hip fracture and breast cancer and nonfatal changes in risk of endometrial cancer. Estimates of reduction in risk of mortality from ischaemic heart disease are inferred from a number of authors who report beneficial effects of tamoxifen on lipid profiles. The findings from the Scottish Adjuvant Trial discussed above suggest a reduction in risk of myocardial infarction of 20%.

They use weaker evidence to derive estimates of changes in hip fracture mortality. Assumptions are based on studies of changes in the bone mineral density of women on tamoxifen though no studies have found any conclusive evidence of a direct impact of tamoxifen on fracture risk let alone mortality. Nease and Ross also assume that tamoxifen will be at least as half as effective as oestrogen in relation to hip fracture risk in postmenopausal women though present little evidence for this view. Since the relationship between oestrogen use, hip fracture risk and mortality from hip fracture is extremely unclear the assumption of a reduction in fracture risk of 25% for all women on tamoxifen is unsupported.

The significance of the change in risk of death from endometrial cancer may be regarded as of less importance in relation to beneficial effects on breast cancer risk since the absolute risk of death from endometrial cancer is low. Increased risk of thromboembolic disease are well documented in women taking tamoxifen and Nease and Ross take their estimate from published studies showing an increase in the range of 3 - 4 fold relative risk. Estimates of reduction in risk of breast cancer mortality of 35% are taken from the early work of the Early Breast Cancer Triallists Collaboration and from the projections set out in the rationale for the NSABP P-1 Breast Cancer Prevention Trial. This is in line with some of the early findings from breast cancer chemoprevention studies.

The analysis from Nease and Ross highlights the importance of baseline risk of breast cancer, the effects of tamoxifen on breast cancer mortality and the effects of tamoxifen on cardiovascular mortality in determining cost effectiveness of chemoprevention. The importance of the effect on cardiovascular mortality can be further illustrated by reference to an English health district population. Prevention trials in general target women at increased relative risk of breast cancer. For a hypothetical population of 400,000 women say between the ages of 35 and 69 around 10% might be expected to be at 3 or 4 fold relative risk of breast cancer with an absolute lifetime risk of between 20 and 30%. This would give rise to between 800 and 1200 cases of breast cancer. If the impact of tamoxifen prophylaxis were to reduce the risk of breast cancer by 30 to 50% a range of 266 to 600 cases might be prevented. Any adverse impact of tamoxifen on serum lipids however would have to be only relatively small to offset this benefit. The average 50 year old women has a lifetime risk of coronary heart disease of about 45% . Increasing the absolute lifetime risk by 1% for the high risk group would result in an additional 400 cases of coronary heart disease. An increase of 2% would considerably outweigh the numbers of breast cancer cases prevented. It has been argued that the latitude over cardiovascular disease effects is small and that even a change in relative risk from 1 to 1.03 would be sufficient to abolish any beneficial effects of tamoxifen[149].

Nevertheless, it seems clear that tamoxifen reduces the hazard of cardiovascular events. A number of authors have shown that effects on lipid profiles occur within 2 weeks of first taking tamoxifen and although the levels appear to return to normal after stopping the benefits may persist[150]. Cuzick et al[145] point out that as cardiovascular benefit is cumulative any period of lowered cholesterol may translate into long term benefits on risks of cardiovascular events. The feasibility of chemoprevention for breast cancer relies on a neutral or beneficial impact on cardiovascular risk for any potential pharmacological agent. Subgroup analysis is also clearly important in this regard since women taking HRT and women at different menopausal status may experience different effects of an oestrogen agonist on lipid profiles.

Economics of tamoxifen chemoprophylaxis

In an economic analysis of chemoprevention in Australia, Butler[13] uses the estimates from the Nease and Ross model described above to derive possible values for the cost per life year gained for tamoxifen prophylaxis. Leaving discounting aside and basing his calculations only on costs for tamoxifen over five years, costs of treating an increased incidence of endometrial cancer and savings from both a reduced incidence of breast cancer and myocardial infarction and from discontinuation of HRT - a requirement of the USA trial - Butler concludes that the net cost of treatment over five years is around $2,500 of which the cost of tamoxifen has the greatest impact on overall cost. The most significant savings in the Butler analysis come from discontinuation of HRT by women taking tamoxifen. The estimates for expected change in the resource intensive outcomes reviewed come from the NSABP P-1.

Taking an 18 day gain in life expectancy from the study set out by Nease and Ross but not including the prospect of being randomised to a non tamoxifen arm, Butler goes on to conclude that the cost per life year saved is over $50,000 (£31,250). If the higher USA costs of tamoxifen are included then the overall cost per year of life gained rises to over $100,000 (£62,500). Increasing the relative risk of women exposed to the preventive intervention reduces the cost per year of life saved. For a 50 year old women at 5x average risk, for example, the estimate falls to around $43,000 (£26,875) per year of life gained.

Different assumptions underpin IBIS. Firstly the costs of tamoxifen in the UK and the rest of Europe is considerably lower than in the USA since patent restrictions on pricing no longer apply. Secondly discontinuation of HRT is not a requirement in the UK study and so the substantial savings estimated for the NSABP P-1 are not relevant. Finally estimates for both the incidence of endometrial cancer and the cost of treatment are high in relation to the change in event rate of breast cancer and the associated costs.

Broad costs of chemoprevention for breast cancer looking solely at the cost of tamoxifen in the UK study are around £120 over 5 years or £24 per women per year taken at a dose of 20mg/day. If the 2% absolute risk reduction in incidence of breast cancer found in the NSABP P-1 applies to the women recruited to IBIS then the cost per tumour prevented is around £6,000. The costs in this simple calculation are based solely on the costs of tamoxifen. They illustrate that the cost of chemoprevention will be affected by the costs of delivering the preventive agent to the number of women who need to be treated in order to prevent one breast cancer (NNT) and the cost of treating side effects in relation to the unit of effect for those who do benefit.

More precise estimates at the cost of morbidity due to long term tamoxifen use are developed in Chapters 4 and 5. Morbidity of women enrolled in IBIS is measured in terms of changes in use of hospital services or prescribed medications respectively for women in the 2 arms of the trial (taking tamoxifen or control).

The following chapter makes conclusions about the likely range of costs involved in delivering a service for tamoxifen chemoprophylaxis. These are based on estimates of the costs of running clinics for women enrolled in IBIS. Directly related research costs are not included.

Summary and Conclusions

The rationale for tamoxifen chemoprophylaxis comes from the mode of action of tamoxifen both as an antioestrogen in suppressing carcinogenesis but also a possible effect on preventing the development of neoplastic agents. Clinical adjuvant studies have shown a reduction in the incidence of new contralateral breast cancers with apparently low overall toxicity from the drug.

Tamoxifen has been seen as the front line treatment for breast cancer since the early 1970s and a number of important studies are available to assess long term outcome including time to recurrence and 5 year survival. Many of these studies have reported on serious side effects of the drug such as deep vein thrombosis & pulmonary

embolism and endometrial cancer. As a result long term breast cancer adjuvant studies are useful in providing information on the safety of trials for tamoxifen prophylaxis but more detailed studies are needed to assess the effect of long term exposure to tamoxifen for chemoprevention of breast cancer in healthy asymptomatic women.

Evidence for the impact of tamoxifen on levels of morbidity which may have consequences for use of health services is scanty both in adjuvant studies and prevention trials. Yet, the impact of tamoxifen on general health and well being may be the key factor in deciding its use for prophylaxis once efficacy has been established. Moreover detailed information on the resource implication for the health service is needed prior to the introduction of an intervention which may have widespread use.

Acute toxicity of tamoxifen is low and prolonged exposure in adjuvant studies does not appear to result in adverse effects on coronary heart disease or bone mineral density despite its anti - oestrogenic properties. In fact, where serum levels of lipids and lipoproteins have been monitored tamoxifen appears to have an oestrogenic effect improving the lipid profile. Various oestrogen - like effects of tamoxifen do however appear to produce premature or recurrent menopausal symptoms.

Evidence from adjuvant studies suggests that the increase in persistent general gynaecological effects from long term tamoxifen use may be around a 25% increase in symptoms sufficient to have an impact on psychological well being. Symptoms may well be underreported in adjuvant studies or more likely to be tolerated by patients than might be expected in a healthy population.

There are concerns about an increase in the relative risk of endometrial cancer for women taking adjuvant tamoxifen. This effect appears to be dose and duration dependant. For women receiving adjuvant tamoxifen at a dose of 20mg per day the relative risk appears to be between two and three fold. Estimates from chemoprevention studies are now as high as a five fold increase though the former

may be explained by the high number of hysterectomies at baseline for women enrolled in the NSABP P-1. The median cumulative dose of tamoxifen needed before diagnosis of endometrial cancer estimated from the Stockholm Trial was 29g. This level would be reached after four years of treatment with a daily intake of 20mg.

There is both clinical and biochemical evidence of an increased risk of thromboembolic events in women taking tamoxifen. The effect is clearly complex and multifactorial influenced also in adjuvant studies by the presence of disease and the impact of chemotherapy. The relative risk for women taking tamoxifen alone either as an adjuvant therapy or for prophylaxis may be between three and five fold although was less than two for all thromboembolic disease in the NSABP P-1. The relative risk appears to increase when tamoxifen is taken in combination with chemotherapy with implications for treatment options; the effect is greater in postmenopausal women.

In terms of benefits of tamoxifen chemoprophylaxis, the impact of long term exposure to tamoxifen on cardiac health may be at least as important as the end point of primary breast cancer reduction. Consistent findings of an effect on lipid lowering may give rise to a relative protective effect of tamoxifen on mortality from myocardial infarction of around 2.0 though the recent updated overview of randomised trials of adjuvant therapy among women with early breast cancer showed no significant difference in the aggregate of all cardiac or vascular deaths after about five years of tamoxifen. The long term impact on cardiac morbidity in general is unclear and will require further research to establish fully. The precise duration of the effect after cessation of tamoxifen treatment is also uncertain.

The impact of tamoxifen on bone mineral density in postmenopausal women seems to be an increase primarily in the lumbar spine and hip by an annual increment of around 1.5% though this increase appears to occur only during the early years of tamoxifen use. Some evidence also suggests that the protective effect on BMD may be lost after cessation of use and similar effects on radial bones appear doubtful. Larger studies are needed to confirm the reduction in bone mineral density in premenopausal women

suggested in results from the Royal Marsden prevention pilot and to assess both the duration of this effect and the clinical significance.

Estimates of the likely reduction in risk of death from breast cancer with chemoprevention have been predicted from adjuvant studies where a review of long term follow up has shown a consistent improvement of around 50% in ten year survival with use of tamoxifen after surgical resection of disease. Consistent with this finding, NSABP P-1 found a 49% reduction in risk of invasive breast cancer in healthy women taking tamoxifen. This has not been confirmed by the publication of two further preliminary reports from chemoprevention studies. Differences in the study populations may may be responsible for these contrary findings.

Chapter Three

Cost of delivering tamoxifen chemoprophylaxis (using the pattern of work and models of service delivery in IBIS centres).

Introduction

This section sets out a range of likely costs for delivering a service for chemoprevention of breast cancer with tamoxifen. The costs are based on the process for care established within the International Breast Cancer Intervention Study. (IBIS)[1] A distinction is made between those costs, which should be primarily attributed to service delivery within the NHS and those which derive primarily from the research protocol. These issues are discussed with conclusions drawn about possible alternative models for service delivery should tamoxifen prophylaxis prove to be effective in reducing incidence and mortality from breast cancer.

Method

A number of models of care have emerged in establishing IBIS within existing routine breast care services. These probably represent the range of options for any future development of preventive care for women at high risk for breast cancer though the structure and function of the IBIS centres has arisen largely from expedience in each of the host services - fitting a research trial alongside busy breast care services - rather than with the economic aim of aim of maximising the efficiency of service provision. Information about costs are derived both from a survey sent to each of the centres and followed up through telephone discussion as well as direct observation on 10 occasions in 4 centres. Additional information was obtained from the IBIS co-ordinator.

Costing information is derived from national pay scales and standard costs for drugs and tests. Comparisons are made between the different possible models of care for delivering tamoxifen chemoprophylaxis based on approaches used in IBIS centres.

Centres and settings for IBIS

At 1 April 1997, there were in the UK 16 centres involved in the IBIS trial with a total accrual of 1,917 women. The rate of women attending the centres who are not subsequently randomised into the trial is low although considerable time can be spent by discussing the trial with women who choose not to be randomised.

Table 1 shows the number of sessions per week run in each of the centres and the setting in which women recruited to the trial are seen .

Table 1 Sessions /week and settings of IBIS Centres

Centres	Sessions per week	setting
Aberdeen	1	ibis*
Belfast	0.25	fh**
B'mingham	1	fh
Bristol	3	g.brst***/fh
Cardiff	3	g.brst/fh
Chelmsford	1	ibis
Edinburg'	1	ibis
Glasgow	1	ibis
Guys	3	ibis
H'dersfield	1	ibis
Leeds	1	g.brst
Leicester	1	fh
Manchester	1	fh
Newcastle	1	fh
Nottingham	1	fh
S'hampton	1	ibis
Total	21.25	
Mean/week	1.33	

* refers to standalone clinic

** refers to IBIS clinic integrated into the family history clinic

***refers to IBIS clinic integrates with general breast outpatient clinic

In general centres run one IBIS session per week though there are three possible sessions in Bristol, Cardiff and at Guys with one each month in Belfast. In at least six out of the 16 IBIS centres women recruited to the trial are seen within family history clinics (fh); in Cardiff and Bristol two further sessions are held alongside general breast care clinics(g,brst). In the remaining six centres IBIS clinics have been established as standalone sessions though working closely with and receiving referrals from the main breast care clinics. In Aberdeen and Chelmsford the IBIS clinics are sited within the breast screening unit.

A broad range of staff are involved in running IBIS clinics. Doctors involved are usually surgeons involved in examining women prior to their recruitment to the trial. Consultant radiologists and geneticists are also closely involved. A number of the centres have the close involvement of clinical assistants or associate specialists who may also be involved in supporting clinics in other parts of the breast care service particularly family history clinics. Nurses working in IBIS are for the most part F or G grade nurses usually with a breast care qualification. A number of the nurses involved are also qualified in research. IBIS sessions in general run with a 1:1 doctor to nurse ratio with other specialist advice available where needed.

The rate of recruitment was lower than anticipated in all of the centres with the possible exception of Bristol which has the highest total number of women enrolled into IBIS and the highest rate of accrual of new recruits. Table 2 shows the average number of new women recruited to each of the centres and the average number of women attending for follow up visits per week.

Table 2: Numbers of new and follow up attendance's/week in IBIS Centres

Centres		
Aberdeen	2.2	8
Belfast	1.5	1.5
Birmingham	3	6.5
Bristol	2.5	8.5
Cardiff	2	6
Chelmsford	1	1.5
Edinburgh	1.5	5

Glasgow	3	3
Guys	2.5	12
Huddersfield	0.5	3.5
Leeds	1	1
Leicester	0.25	1
Manchester	1.5	13.5
Newcastle	0.25	3.5
Nottingham	1	3
Southampton	2.5	6.5
Total	**26.2**	**84**
Mean/week	**1.64**	**5.25**

An average of around 1.6 new women are seen per week with a range of 0.25-2.5 depending on the size of the clinic. Although the time involved in seeing women for follow up visits is considerably less than that for new recruits the follow up visits represent a considerable workload for the centres because of the numbers and total amount of time involved. The average number of follow up visits per week is 5.25 with a range of 1-13.5 depending on how long the centre has been running.

Women are seen 2x per year according to the schedule set out in the IBIS protocol. The time spent with new recruits varies between the centres though is on average about 3x higher for new visits than for follow up visits. Table 3 shows the estimated mean time spent with women on the first and subsequent visits across all centres.

Table 3: Time (mins) spent with patients (mean (std dev))

	New Visits	*Follow up visits*
Dr	23(16)	5(4)
Nurse	36(28)	14(9)
Total	59(44)	19(13)

At the initial visit the trial is discussed with the woman and any questions answered in detail either by the nurse or the doctor depending on the usual practice in the centre. In most centres initial enquiries about the trial are made outwith the clinic session and the time involved is not included here since it does not relate directly to service

delivery. Once the women have consented to participate in the trial a randomisation number is obtained from the IBIS office at the Imperial Cancer Research Fund (ICRF) and the recruitment process takes place. A complete clinical history is taken along with measurements of height, weight and blood pressure according to the IBIS protocol. Women have a mammogram at the initial visit unless they have had one within the last 12 months.

A blood test is also taken at this visit which the nurse spins and sends to St Mary's NHS Trust for analysis for cholesterol levels; no other test is made though the bloods are stored for subsequent review of compliance or further tests should they be needed. The women are provided with supplies of tablets (tamoxifen or placebo) according to randomisation and future appointments are made. Written information is given to all patients with a telephone number for queries or concerns. Supplies of tamoxifen or placebo are counted, prepared and stored either by the IBIS nurse or co-ordinator though in some centres the pharmacy department take responsibility themselves for storing and dispensing.

Most of the activities undertaken for the initial visit within IBIS would be the same within routine service delivery. Activities such as randomisation and discussion of the aims and objectives of the trial would not of course take place in an NHS clinic. The former is however a small part of the overall time taken at the initial visit and the latter would be equivalent if adopted in routine practice to time spent describing the evidence on which the prophylaxis was being offered.

Staff Costs

Table 4 shows the estimated staff costs per new patient visit per centre. The costs are based on the number of new patient visits and incremental costs of staffing the sessions assuming £300 per consultant sessions, £100 per clinical assistant session and £50 per nurse session. The length of each session is taken as 3 hours. The secretarial/administrative costs are not included at this stage since they vary considerably between the centres. Moreover many of the tasks involved in advertising

the trial and recruiting women are not included here since they relate to the running of IBIS and are not relevant to routine service delivery.

Table 4: New Recruits - Staff Costs

IBIS	*Doctor*							
Centre	Specialty	mean time (m)	*number new*	*Dr cost*	Nurse	time spent	*nurse*	*Total staff** cost*
		per woman	*women/week*	*	*grade*	*by nurse(m)*	*cost#*	*per new recruit*
1	rad/altsurg/onc	45.00	2.20	162.36	d	5.00	1.21	74.35
2	surg	10.00	2.00	32.80	h	20.00	12.30	22.55
3	scmo	25.00	3.00	41.25	h	10.00	12.30	17.85
4	scmo/surg	2.00	2.50	8.20	g	15.00	11.63	7.93
5	surg	30.00	2.00	98.40	f	120.00	50.40	74.40
6	surg	5.00	1.00	8.20	f	15.00	3.15	11.35
7	genetics	35.00	1.50	86.10	f	45.00	20.93	71.35
8	surg	10.00	3.00	49.20	h	40.00	37.20	28.80
9	surg	40.00	2.50	164.00	g	45.00	34.88	79.55
10	surg	0.50	0.50	0.41	g	30.00	4.65	10.12
11	surg	20.00	1.00	32.80	f	60.00	18.60	51.40
12	ass spec	10.00	0.25	1.38	f	20.00	1.05	9.70
13	oncol/gen	15.00	1.50	36.90	f	20.00	6.30	28.80
14	gp/surg	30.00	0.25	4.13	f	45.00	2.36	25.95
15	sr/clin asst/surg	50.00	1.00	27.50	g	50.00	15.50	43.00
16	clin asst	40.00	2.50	55.00	2xg	40.00	62.00	46.80
Total		367.50	26.70	808.62			294.45	41.31
mean		22.97	1.67	50.54		0.00	18.40	41.31
std dev		16.10	0.93	52.32		27.60	18.45	76.28
*at £300/consultant session								
#at £50/Nurse session								
**Dr and nurse only								

1

The mean costs per new patient are just under £42 , the range is from £8 in centre 4 to almost £80 in centre 9. The variation in costs per new patient are explained by the difference in doctor time spent with new patients . Costs are directly proportional to the amount of time spent by doctors irrespective of the differences in costs of doctor time between grades. Lower costs are found in centres where nurse involvement

[1] Advance letter April 1995 NHS(E)
Nursing and Midwives NM 1/1995
Doctors and Dentists MD 1/1995

occupies the greatest proportion of time spent by clinical staff. In centres such as Guys, Aberdeen, Cardiff and Edinburgh where doctors spend relatively more time explaining the trial and the process of care for women involved costs are higher.

The process of care in IBIS is well illustrated by the centre with the highest rate of recruitment to the trial. This centre also has the lowest cost per patient. Until recently this centre was based only in the family history clinic. The nurse discusses the trial with women referred from either the family history clinic or from general practitioners. She also completes the history for entry to the trial, takes blood and secures referral for mammography. The doctor examines the patient between routine consultations within the general clinic. On occasions staff in training grades are available to support this process and may be able to examine women recruited for IBIS. In general the surgeon's time is not much reduced by this process since queries can take a good deal of time and trainees are likely to see far fewer women than the consultant. More recently a clinical assistant has been recruited to support the general clinic and is available to see IBIS women. Again, in general the clinical assistant sees fewer women than the consultant and takes longer. Queries are discussed with the consultant. Routine ultrasound is offered to women in this clinic yet the costs in terms of doctor time are not affected. Follow up costs in terms of clinical staff time are shown in table 5 below:

Table 5. Follow up staff costs per woman

IBIS	number				Cost	Total cost
Centre	f/u per week	nurse t(m)	Cost Nu t(£)	Dr t (m)	Dr time	Dr&Nu (£)
1	8.00	17.50	15.40	2.00	26	42
2	1.50	20.00	12.30	2.00	5	17
3	6.50	1.00	2.67	5.00	18	21
4	8.50	15.00	39.53	5.00	70	109
5	6.00	25.00	31.50	2.00	20	51
6	1.50	10.00	3.15	2.00	5	8
7	5.00	15.00	15.75	15.00	123	139
8	3.00	20.00	24.60	2.00	10	34
9	12.00	10.00	37.20	10.00	197	234
10	3.50	10.00	10.85	0.50	3	14
11	1.00	15.00	3.15	10.00	16	20
12	1.00	0.00	0.00	10.00	6	6

13	13.50	25.00	70.88	1.00	22	93
14	3.50	12.50	9.19	5.00	29	38
15	3.00	30.00	27.90	3.50	17	45
16	6.50	15.00	60.45	2.00	21	82
Total	**84**		**365**	**77**	**587**	**952**
Mean	**5**		**23**	**5**	**37**	**59**
Std dev	**4**		**21**	**4**	**52**	**61**

Overall the follow up visits during the week increase the total cost per new recruit per week by a factor of about 1.5. The numbers of follow up visits quickly accrue particularly in centres with a high rate of recruitment. The time spent with women during follow up visits by both the doctor and nurse is however considerably less than with women new to the study. The amount of time spent with the doctor is still the main factor explaining the cost differences between the centres. The centres with the highest follow up costs are those where medical staff spend a large proportion of the total time of the visit with the patient. Where doctor time is also relatively higher in centres such as 11 and 12 with lower overall costs this is because of the lower grade of the doctor involved. Clinical assistants and associate specialists are responsible for IBIS patients in five of the centres.

This analysis has focussed on costs most likely to influence the cost effectiveness rates for tamoxifen chemoprophylaxis. Where breast cancer chemoprevention was to be introduced into routine services fixed costs would need to be considered. This study demonstrates however only a small increase in the proportion of women seen compared with the overall numbers attending breast services. Moreover where service delivery was offering in general practice changes in fixed costs to women attending for chemoprevention would be negligible.

There are a number of hidden costs involving staff time which could be attributed to IBIS because they may bear on the overall costs of the trial; they are less likely however to play a significant role in service delivery. These include the time spent discussing the trial with potential new recruits in settings other than those designated for the study. In some hospitals the trial is discussed extensively with eligible women

attending genetics clinics, particularly those under 50; one centre estimates that only 1 in 8 women decide to become involved in the study though about 3-5 eligible women are seen per week and a substantial amount of time is spent with them. Another centre based in a screening unit asks women if they have a family history of breast cancer in order to assess eligibility for IBIS. Where eligible women are identified they are referred to the IBIS clinic but only via a referral to the genetic clinic. Direct costs which can be attributed to IBIS from general practice emerge in one centre where women are routinely referred back to their GPs for breast examination.

In most centres the hospital pharmacy has been helpful in storing, counting and dispensing tablets though there have been concerns about funds available to support this work. Where pharmacy has been unwilling or unable to store and process supplies the centre co-ordinator or nurse has taken on this task.

A considerable amount of time is spent in writing to or phoning women who have expressed an interest in the study, or those who have missed an appointment or have a particular problem. Most centres also contact women prior to appointments or to follow up an initial discussion since this is thought to be an efficient means of screening out those women who are unlikely to pursue the study and to reduce the rate of missed appointments. Centre co-ordinators also spend time working through the press or within local networks seeking to publicise the study and to encourage new recruits. A range of estimates are reported from centres on the time spent on these activities although all report the need to increase the time available for recruitment. In general it might be expected that an additional three-hour session of clerical time may be needed. This would increase the cost by around £13/new patient visit. This cost is excluded from the analysis since it is a research cost rather than directly attributable to service delivery.

Costs of tests and drug supplies

Additional costs (see table 6) include an annual mammogram at around £56, blood tests taken at the beginning and end of the study costed at £10 in total and drug

costs[166]. Other consumables including equipment used during in examination and set up costs for the clinic are omitted since they are unlikely to add substantially to the cost of clinic visits. Tamoxifen is a relatively inexpensive drug and at around £30 per year will represent a small proportion of the total overall costs. The cost for each new patient visit is around £81. The average cost for follow up visits is around £33.8.

Table 6: Costs of Tests and Drug Supplies (£)

For women in IBIS					
Visit		Mammography	Blood	Drugs	Total (new)
1		56	10	15	
	Total new	56	10	15	81
Follow up month					
6		0	0	15	
12		0	10	15	
18		56	0	15	
24		0	0	15	
30		0	0	15	
36		56	0	15	
42		0	0	15	
48		0	0	15	
54		56	0	15	
60		0	10	15	
	total f/u	168	20	150	338
	£/per fu visit	16.8	2	15	33.8

Costs per woman per five year recruitment

The staff time costs set out above together with the costs of drugs investigations and mammography outlined above are used to derive an estimate of the overall cost for delivering tamoxifen chemoprophylaxis per woman. This is set out in the table 6.

Estimated cost per woman recruited to IBIS				
Item	£/episode	over 5 years	%	
Mean staff cost (new recruit)	42.00	42.00	4%	
Mean staff cost(follow up visit)	59.00	590.00	53%	
Tests, investigations (new recruits)	66.00	66.00	6%	
Tamoxifen prescriptions(new recruits)	15.00	15.00	1%	
Test, investigation (follow up)	18.80	188.00	17%	
Tamoxifen(follow up)	15.00	150.00	13%	

Administration cost/woman/year			13	65.00	6%
	Total			1116.00	100%

The overall cost per woman over the 5-year period of taking tamoxifen is around £1000 per woman. The cost of recruitment (4%) is a relatively small proportion of the overall cost of offering tamoxifen chemoprophylaxis. Staff costs for time involved in follow up visits accounts for by far the greatest proportion of the overall cost (53%). The costs of prescription and investigations(mammography and blood tests) account for a similar proportion (around 15% and 17% respectively)

Discussion

The costs discussed here based on the amount of time spent by staff involved in delivering tamoxifen prophylaxis together with the costs of mammography and routine blood tests. Only costs, which are clearly associated with service delivery, are included. Costs attributable to the context of a research trial are excluded. These include the time spent outwith clinic sessions discussing the trial with potential recruits, time spent in talking with women's groups or press activity. The time spent in randomisation is likely to be small in terms of the overall time spent recruiting women. Discussion about the trial, which takes place within the clinic session, may be assigned as a research cost but would be equivalent to time spent discussing the rationale and evidence for prophylaxis with women in a service context.

Fixed costs are not included since they would be likely to vary considerably between centres irrespective of the model of care for IBIS. The overall cost of service delivery at less than £200 per new women per year recruited is relatively low in comparison with many other areas of health care. This level of cost might be considered equivalent to outpatient costs for some medical specialties where there are few expensive investigations and the costs of medical therapies are low. The difference between the cost of routine service delivery and the research protocol is likely to be small since there are relatively few investigations for women recruited to IBIS other than annual mammography. Blood tests are taken only at the beginning and end of the recruitment period. Routine endometrial screening and other tests undertaken in

the NSABP P-1 study[2], which would considerably increase the difference in costs between the research and the clinical setting, are not included in the IBIS protocol.

It is possible however that in the context of a clinical trial more frequent follow up and investigation might be considered necessary than for routine service provision. Women involved in chemoprevention of breast cancer may potentially require minimal investigation. Even annual mammography for example required within the trial protocol may be inappropriate within the context of service delivery. The evidence for improved health outcomes with frequent mammography screening for women under 50 is poor and women over age 50 would have access to mammography as part of the NHS Breast Screening Programme (every 3 years until age 65). Such an approach would also reduce overall costs and the pressure on mammography services.

The amount of time spent by specialist breast surgeons either in breast examination or in providing information to women about the risk and benefits of tamoxifen prophylaxis accounts for the greatest proportion of staff cost. If this task were appropriate to be performed by a nurse with specialist support staff costs could be much reduced. Such an approach is within the range of models of service delivery currently used within the IBIS trial protocol and might be adopted with minimal additional training for nursing staff within the umbrella of breast care services in the UK. Where the service is led by nurse practitioners minimal input from a consultant surgeon may be reduced to a single session to discuss the risks and benefits of tamoxifen prophylaxis in terms of individual level of risk of breast cancer. Such an approach with nurse only follow up visits and mammography reduced to 3 times over the course of the 5 year period of active prevention would reduce costs per woman to around £535 over the 5 year period. The burden of cost likely to fall on breast units adopting this approach would depend on the numbers of additional women eligible for prophylaxis and willing to comply with long term drug treatment - and the marginal increase in numbers of women within the breast service likely to increase the demand for additional members of clinical staff and clinic sessions.

The pattern of service delivery may well be more appropriate to general practice than to most hospital care possibly with referral for specialist support should problems or anxieties arise. In practice symptoms or signs emerging during the course of prophylaxis are likely to be dealt with in primary care or referred on by GPs to appropriate specialists. Evidence from other areas of health care suggests that there is little value in routine follow up visits to specialist centres. Where general practice were to be considered a more appropriate setting particularly for follow up visits costs may reduce to around £410 per woman over the 5 year period assuming as in the nurse led model a single visit to a specialist breast surgeon and 5 annual visits to a GP. Most GPs would expect to see only 2 or 3 women per year with the eligibility for tamoxifen prophylaxis and the motivation to undertake long term drug therapy.

These issues are discussed further in Chapter 7 where a consolidated estimate for cost effectiveness is modelled from the costs set out in this and subsequent chapters. The baseline estimate for the cost of service delivery used in the model is of a hospital based service led by consultant breast specialists though with significant involvement of specialist nurses (£535/woman) as described above. Sensitivity analysis does however include other estimates including the possibility of a service delivered through general practice at £410/woman and with the lower estimates of £200/woman underpinning the budgets available to centres within IBIS

Summary and Conclusions

Costs for service delivery are based on a direct observation and a telephone survey of workload, staffing and the clinical protocol used in IBIS centres. Costings are based on bottom up assessment of the time spent by staff with IBIS recruits using national pay scales. Mammography is costed at £56, blood tests at £10 in total and the cost of 20 mg tamoxifen daily is taken as £15 per year from the National Drug Tariff. The overall cost for delivering tamoxifen prophylaxis within the context of the trial is £1116 per woman per 5 years. The largest proportion of cost (57%) is in staff time. The cost of doctor time is the largest element; the amount of time spent by the doctor

explains the difference in cost between the centres. Tests and investigations account for a further 23% of the cost and provision of the drug tamoxifen for 14% of the cost. Costs of administration make up the remainder of the cost (6%)

Hidden costs are discussed and include the time spent discussing the trial by other health professionals particularly geneticists running family history clinics and GP time. In one centre for example the physical examination is carried out by the GP.

The review illustrates that there is little specialist input to the provision of tamoxifen prophylaxis and that the main time element is in discussing the concept to the women and the protocol for consent to enter the trial. While the time element in 'consenting' woman may translate into time spent discussing the evidence base and side effects of tamoxifen prophylaxis if the approach was adopted in routine practice some savings could be made.

Leaving aside the research costs included in the overall estimate and reducing the time spent by women in the clinic as well as some of the investigation two scenarios for service delivery are proposed. These are £535 for a nurse led hospital service or £410 for a service run in general practice. The hospital service is used as the baseline approach for the model developed in chapter 7 and the GP run service is explored through the sensitivity analysis. Both approaches would rely on minimal input from a consultant surgeon or equivalent with only 1 visit included for the 5-year period. The frequency of mammography would reduce to a maximum of 3 times in the 5-year period. Both scenarios exclude the costs attributable to the research trial particularly the need for annual mammography, the taking and processing of blood and time spent recruiting women to the study.

Chapter Four

Morbidity and Resource Use:

Use of Hospital Services

Introduction

Following the review of literature about the risks and benefits for women taking the drug tamoxifen in Chapter 2, this and the following chapter derive more precise estimates of the likely impact of morbidity on the cost effectiveness of tamoxifen chemoprophylaxis. This chapter is concerned with the prospect of changes in the use of hospital visits for symptoms associated with long term tamoxifen use and Chapter 5 measures changes in the rate of use of prescribed medications. The analysis is based on measurements of differences in the morbidity experience of women in the tamoxifen or control arm of the International Breast Cancer Intervention Study (IBIS).

Small changes in the use of hospital services or prescribed medications for the age group targeted in prevention trials could have a significant impact on overall cost if large numbers of women were affected. Yet, there have been few studies published on the effect of tamoxifen on morbidity as measured through changes in hospitalisation rates or use of medications. As discussed earlier there have been great many studies of the effects of tamoxifen when used as adjuvant therapy.

Most prevention studies have been primarily concerned with the effects of tamoxifen on adverse outcomes such as thromboembolism or endometrial cancer. Primary endpoints in NSABP P-1[2] and in the Powles[8] and Veronesi[11] studies all include incidence and mortality from histologically confirmed breast cancer. Other incident cancers including endometrial cancer are also recorded and all causes of death during the trial verified. Secondary endpoints include ischaemic heart disease events, other vascular events and fractures. 'Other disease' and medical problems are sometimes recorded at each visit yet there has been no systematic reporting of morbidity from these studies.

Fornander et al[142] considered the impact of adjuvant tamoxifen on the intercurrent morbidity and mortality of women involved in the Stockholm Adjuvant Trial using

information on hospital admission records and death certification but no studies have reported the detailed pattern of hospital use by women involved in prevention studies or their use of prescribed medications for conditions relevant to known side effects of tamoxifen or for their health in general.

Women may experience symptoms arising directly from the use of tamoxifen necessitating a hospital referral or the use of a drug or by contrast they may experience a reduction in the frequency of morbidity because of a protective effect of prophylaxis. Changes in the pattern of morbidity may also arise indirectly from different health behaviour elicited by involvement with a preventive intervention. Women taking long term preventive therapy may be more likely to seek medical advice as a result of heightened awareness of their risk of disease; greater personal awareness of health and illness may reduce their threshold for consultation about relatively minor symptoms. Alternatively they may feel more reassured by the fact of the preventive intervention and reduce their use of health services. Women recruited to IBIS for example may make use of routine consultations with health care professionals at IBIS clinics for discussion of broader health issues and as a consequence reduce their use of other health facilities.

Quite apart from the relatively rare adverse outcomes from tamoxifen therapy there are common side effects which may have consequences for the pattern of morbidity in patients treated with tamoxifen over a long period of time. These side effects may affect both compliance with prophylaxis in healthy women who are otherwise asymptomatic for breast cancer or related diseases and if translated into use of health services or the rate of prescribing may influence the relative cost effectiveness of chemoprevention. Information from women recruited into IBIS is used in this section to identify and quantify this effect through measuring changes in the use of hospital services by women recruited to IBIS.

Method

The information presented below is collected from self-reports of hospital visits made by women recruited into IBIS. Women are asked at recruitment, at the first follow up visit at 6 months and at each of the subsequent visits at 6 monthly intervals over the 5-

year duration of the trial about any hospital visit. A brief outline is requested on the data collection form and the study co-ordinators in each centre are asked to forward details on an illness report form together with any confirmatory information including pathology reports or copies of correspondence between GPs and hospital consultants.

Information on the use of hospital services since the previous visit is also occasionally recorded on the section of the follow up form requiring details of side effects. This covers a range of usual symptoms and includes a request for details of 'other' symptoms where information about hospital use is sometimes entered. All information on hospital visits from the follow up forms is entered into an oracle database by data entry clerks.

The information selected to assess the hospital resource use included all women recruited to IBIS who had a hospital visit by the end of December 1997. Completeness and accuracy of the follow up entries for the women was checked through hand searching of the patient records. A great many incomplete records were found necessitating validation and completion of the information by reference to the woman's original notes or through discussions with the study centre co-ordinators. The data were downloaded to an Excel spreadsheet for each of the women reporting hospital use and then summarised to produce where possible a diagnosis using 3 digit codes from the International Classification of Diseases 9th series (ICD9) and main ICD9 chapter headings for the diagnosis given on the form.

Since the main aim of the study was to assess any change in use of health services by women taking tamoxifen for breast cancer prophylaxis it was important to quantify the use of health care resources arising from hospital visits. This was done by assigning each of the procedures recorded in the notes to a health care resource group (HRG) [15]. The HRGs are readily costed with standard prices from the District General Hospital Accounting System used within the National Health Service (NHS)[166]. HRGs were developed by the National Case Mix Office funded by the NHS. They aim to provide a straightforward means of assigning hospital admissions including both day case and inpatient episodes into clinically meaningful groups representing similar levels of health care resource consumption. The main value of HRGs is that they include case mix information and so can provide appropriate

comparison for assessing the efficiency of resource use between different hospitals. Case mix adjustments include the age of the patient and the presence of comorbidities or secondary diagnosis in relation to the main condition under review. The use of HRGs in this study is to derive a likely cost for each hospital visit that is based on more detailed information than diagnosis or procedure code alone. Costs can vary considerably depending on the severity of the condition, the age and general health of the patient. A number of studies have use of HRGs in predicting cost differences between hospitals and they have been adopted as the main means for costing health care contracts in the NHS.[167,168,169,170]

Hospital visits involving any clinical procedure in the 6 months prior to each IBIS follow up visit had an HRG assigned to them where possible using the primary diagnosis from the information given on the women's record, the procedure and the age of the woman. Each assignment was checked by a general practitioner advisor to the National Case Mix Office and a reference set of HRGs established for the most frequent symptoms and information found within the records. In the main the final set of HRGs included in the analysis presented here include only those which would normally be classified in the routine information from the NHS as 'inpatients' or 'day cases'. Out patient visits do however increasingly result in the use of procedures such as endoscopy or breast biopsy and where possible an HRG has been assigned to them. The information included under the heading of outpatient activity therefore includes only those cases where no specific procedure was reported for example where the woman may have been offered advice, given a test result (recorded at a previous visit) or referred back to her general practitioner. These 'outpatient episodes' have been costed using GP Fundholders price tariffs from the specialty reported on the record or that most usually associated with the diagnosis or procedure[166].

In order to preserve the blinded nature of the IBIS trial the data have been separated into 2 groups: A and B for women taking either tamoxifen or placebo; the 2 groups are anonymised and do not label the same arm of the trial throughout this analysis. It was not possible to assign an ICD 9 Chapter to 68 of the visits reported, 33 in group A and 35 in group B. For 9 women - 5 in group A and 4 in group B it was unclear whether a procedure had taken place as a result or their visit to hospital. For these women hospital expenditure of £100 was assumed since it was clear from the record

that they must have incurred at least an outpatient visit. For 2 women, pregnancy was the reason for the hospital visit. Since pregnancy is unlikely to have been affected by tamoxifen chemoprophylaxis but immediately excludes the woman from further participation in the study they have been excluded from the final analysis.

Statistical analysis

For all women recruited to the trial descriptive information on the use of hospital services is grouped and ranked according to the number and proportion of visits by main reason for visit within main ICD9 chapter heading, for specific diagnosis associated with 3 digit codes) and by main procedure undertaken (HRG). The number of visits per woman is also calculated overall and per follow up visit. A frequency distribution of the cost of hospital visits is used as the most suitable means to demonstrate the shape of the cost distribution.

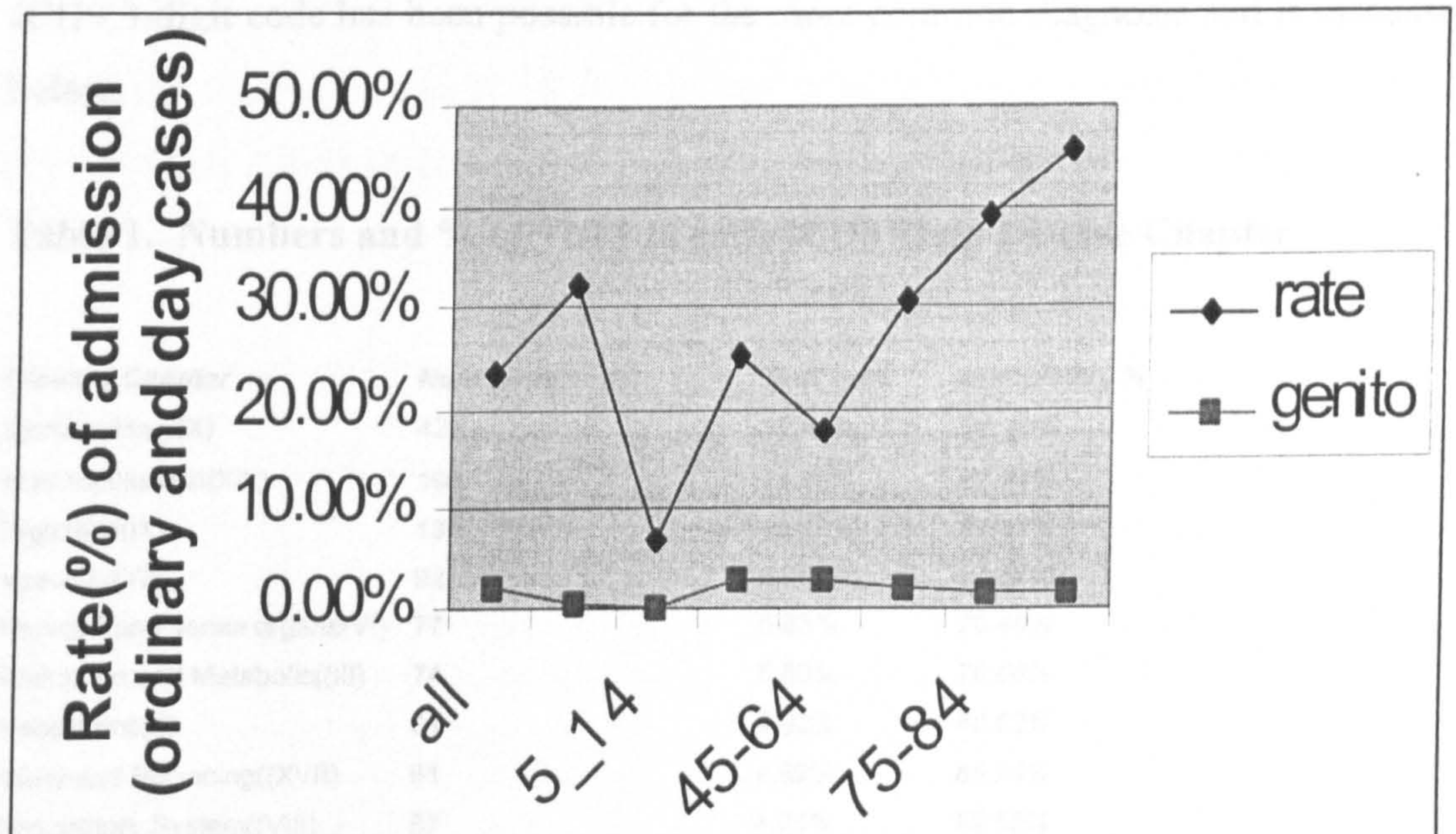
Differences in the rates of use of hospital both by diagnosis category and for procedures undertaken are calculated as odds ratios with confidence intervals calculated by the standard method of Cornfield. Comparisons of the mean cost per visit overall in each of the 2 series is calculated with Fishers exact test using a normal approximation. The size of the sample and the shape of the distribution may affect the significance of the finding between the 2 series. Once a larger sample is available consideration may be given to a Wilcoxon Sum test to account for the non normal shape of the distribution of costs to women although as the sample size increases the conditions for assuming a normal distribution increase. Applying the test at this stage would have discerned no further information. A student's t test was used to compare the distribution of costs per women within each of the disease categories. A non parametric test on ranked data may have been more appropriate although the distribution of costs per women within disease categories more greatly approximates a normal distribution than seen in the overall costs.

Results

Women recruited to IBIS: broad patterns of hospital use

Out of the *2531* women recruited to the study with a total of 6696 IBIS follow up visits at the time of analysis a total of 825 (32.32%) women reported 1321 hospital visits since their previous assessment at an IBIS clinic; a rate of 1.6 visits per woman. There were 814 outpatient visits where no procedure was undertaken and 507 visits made by 429 women (16.9%) included procedures which could be assigned to an HRG. By comparison, the rate of admission either for a day case or an ordinary in-patient admission to an NHS hospital in 1994/5 was around 17.8% of women aged 45-64 (see fig 1) [167].

Fig 1. The rate of admissions to NHS hospitals (ordinary and day cases) for all women in England. The rate of all admissions is shown (rate) and the rate for genitourinary (genito) conditions only.



Women in the 45-64 age group most likely to be targeted for breast cancer prophylaxis are relatively high users of hospital and other health services for

conditions associated with breast care and genitourinary problems though they have a lower overall rate of admission than both older and younger adult women. The higher rate of admission to hospital for all conditions in younger women (aged 15-44) is due to pregnancy and childbirth. Older women in the age groups 65-74 and 75+ have the highest rates of admission for all causes, these are principally due to cardiovascular conditions, cancer and other chronic diseases such as respiratory problems and diabetes.

The mean age of women recruited to the study overall is 49.5 years compared with a mean of 49.8 years in series A and 49.1 years in series B. The median time of follow up was 18 months. Table 1 shows the main reasons for attending hospital by all women reporting a hospital visit. In the table all diagnosis are grouped for all women under the main ICD9 chapter headings since it is expected that tamoxifen may have similar effects in similar body systems. Also, there are small numbers in some of the specific disease categories and review of broader groupings may allow more meaningful statistical analysis. Some analysis of specific diagnosis at the level of ICD9 3-digit code has been possible for the more common diagnosis and is discussed below.

Table 1. Numbers and % of Visits in each ICD9 Main Disease Chapter

Disease Chapter	*Number of Visits*	*% of total*	*Cumulative %*
Genitourinary(X)	429	32.48%	***32.48%***
Musculoskeletal(XIII)	195	14.76%	***47.24%***
Digestive(IX)	137	10.37%	***57.61%***
Vascular(VII)	92	6.96%	***64.57%***
Nervous and sense organs(VI)	77	5.83%	***70.40%***
Endocrine and Metabolic((III)	74	5.60%	***76.00%***
Neoplasms(II)	61	4.62%	***80.62%***
Injury and Poisoning((XVII)	61	4.62%	***85.24%***
Respiratory System((VIII)	57	4.31%	***89.55%***
Skin(XII)	31	2.35%	***91.90%***
Infectious(I)	17	1.29%	***93.19%***
Mental disorders(V)	14	1.06%	***94.25%***
Blood(IV)	5	0.38%	***94.63%***
Unassigned	71	5.37%	***100.00%***
Total	**1321**	**100.00%**	
Number of women	**825**		
Mean age of women	**49.5years**		
Median follow up	**18 months**		

Overall, the main reason for hospital visits accounting for over a third of the total (32.4%) fall into Disease Chapter 10 - diseases of the genitourinary system covering disorders of the female genital tract, urinary tract and breast diseases. Musculoskeletal disorders including fractures form the second major category of reasons for visits (14.7%). Diseases of the digestive system account for 10.3% of the total visits and diseases of the circulatory system covering cardiological and vascular disease account for 6.9% of visits. Diseases of the endocrine and metabolic system, the nervous system including sense organs, injury and poisoning including fractures and the respiratory system each account for less than 6% of the reasons for visits and 5% were unclassified; 4.6% of the women had visits due to neoplasms.

The distribution of hospital visits by main ICD9 Disease Chapters for women recruited to IBIS overall is similar to that found in the NHS routine admissions data (ordinary and day cases) although the NHS routine data do not include outpatient visits (Table 2).

Table 2: Number and % of Admissions (Ordinary and Day Cases) to NHS Hospitals in England (1994/5) by main ICD9 Disease chapter for Women aged 45-64.

	Admissions		
Disease Chapter	**ordinary and day cases**		
	Numbers	**%**	
Neoplasms	**160534**	**15.58%**	
Genitourinary	156835	**15.22%**	
Musculoskeletal and injury	142393	**13.82%**	
Digestive	125722	**12.20%**	
Vascular	96426	**9.36%**	
Nervous and sense organs	56512	**5.48%**	
Respiratory	41248	**4.00%**	
Mental disorders	28145	**2.73%**	
Skin	25144	**2.44%**	
Endocrine and metabolic	18412	**1.79%**	
Blood	11584	**1.12%**	
Infectious	6968	**0.68%**	
Other	160775	**15.60%**	
TOTAL	1030698	**100.00%**	

The largest category in the NHS admissions data is women admitted for neoplasm - these women would be ineligible for recruitment to IBIS. Apart from this category the ranking of reasons for hospital attendance is broadly the same by main ICD9 chapters for both women reporting hospital visits in IBIS and women in routine NHS data.

The proportions in the 2 series are not directly comparable. NHS data are based on hospital episodes rather than individual visits. The routine NHS data do not include information on outpatients although they do cover a rather broader range of reasons for admission than is seen for women in IBIS. Nevertheless it is interesting to note that women enrolled in IBIS appear to report the use of hospital services for genitourinary conditions at a higher rate than seen for women in the NHS data set. 238 women out of the 2,531 women recruited to IBIS (9.4%) reported a visit to hospital including a procedure categorised within an HRG in the disease chapter concerned with genitourinary conditions compared with a consultation rate seen in the NHS for these conditions (see fig 1) of 2.71%. By contrast the reported rate of consultation for musculoskeletal conditions, the second highest reason for hospital use by women in IBIS was similar to that seen in the NHS data set. There were 62 women out of the 2,531 reporting a visit involving a procedure in this group, a rate of 2.4%. This compares with around 2% in the NHS data set (113,612 admissions including ordinary and day cases out of a population of 562,4364 in the relevant age group). The comparison is imprecise since the 2 data sets are not directly comparable though the indication of an increased rate of consultation by women recruited to IBIS merits further investigation.

Comparison between the use of hospital services by women in IBIS and the pattern of admissions for women in England does offer face validity to the IBIS data set. The range and ranking of hospital visits seen for women enrolled into IBIS are as might be expected from routine sources.

Main diagnosis within disease chapters

The tables below show the specific diagnosis based on the 3 digit ICD9 code which contribute the greatest overall proportion of hospital visits for each of the main chapter headings.

Diseases of the Genitourinary System

For diseases of the genitourinary system, the most frequent cause of any hospital visit, almost a third of hospital visits are due to disorders of menstruation and other abnormal bleeding from the genital tract. Slightly more than half is for diagnostic procedures such as hysteroscopy - or for hysterectomy. A further 20% of visits are due to disorders of the breast including fibroadenoma, cysts and benign lumps as well as inflammatory disease of the uterus (615) such as fibroids or secretory changes in the endometrium and inflammatory disease in the cervix, vagina or vulva. The remaining causes include problems of pelvic floor, abnormalities resulting from prolapse (618) and other symptoms such as pain and urethritis.

Table 3: Hospital visits made by women recruited to IBIS: Diseases of the Genitourinary System by main cause.

Main primary diagnosis for diseases of the genitourinary system			
	Numbers	%	Cumulative %
Disorders of menstruation (626)	129	30.07%	30.07%
Disorders of the breast(611)	87	20.28%	50.35%
Inflammatory diseases of the uterus(615)	47	10.96%	61.31%
Inflammatory diseases of the cervix, vagina, vulva(616)	34	7.93%	69.23%
Genital prolapse(618)	24	5.59%	74.83%
other	108	25.17%	100.00%
Total	429	100%	

Diseases of the Musculoskeletal system

The main diagnosis for women with musculoskeletal conditions is shown in Table 4. Back problems account for the highest proportion of visits. Other arthropathies account for a further 10%. Osteoarthritis and other joint disorders make up around 8% each.

Table 4: Hospital visits made by women recruited to IBIS: Diseases of the Musculoskeletal System

3 digit code	*Diagnosis*			*Numbers*	*%*
724	Disorders of the back			41	21.03%
716	Arthropathies			20	10.26%
715	Osteoarthritis and allied disorders			17	8.72%
717	Internal derangement of knee			17	8.72%
727	Disorders of tendon and synovium			16	8.21%
714	Rheumatoid arthritis			15	7.69%
722	Intervertebral disc disorders			14	7.18%
	Other			55	28.21%
	Total			195	

Diseases of the Digestive System

Table 5 shows the main reasons for attending hospital with digestive disorders. Cholelithiasis is the main specific diagnosis accounting for around 20% of the reasons for visits in this group. Other less specific diagnosis have been classified under 537 for disorders of the stomach and duodenum including hiatus hernia and celiac disease or under 564 covering pain and other symptoms in the lower abdomen. Together these 2 diagnoses make up about 35% of the total. Other conditions reported include, for example, 7 women with diverticulitis, 4 women having 6 visits due to gastrointestinal haemorrhage and 4 women admitted with acute appendicitis.

Table 5: Hospital visits made by women recruited to IBIS: Diseases of the Digestive System

3 digit code	Diagnosis	Numbers of visits	%
564	Digestive disorders	33	24.09%
574	Cholelithiasis	28	20.44%
537	Disorders of stomach and duodenum	15	10.95%
530	Disorders of oesophagus	7	5.11%
562	Diverticula of intestine	7	5.11%
520	wisdom tooth problems	6	4.38%
578	Gastrointestinal haemorrhage	6	4.38%
577	Disease of the pancreas	5	3.65%
	Other	29	21.17%
	outpatient	1	0.73%
	Total	137	100.00%

Diseases of the Vascular System

The largest proportion of visits for vascular conditions are for varicose veins(25%) (see Table 6). There were also 13 visits for angina and 11 for hypertension. Other forms of heart disease and heart failure account for a further 15% of the visits. A total of 6 visits were recorded for venous embolism and venous thrombosis with a further 2 visits for thrombophlebitis and 2 for peripheral vascular disease. There was 1 subarachnoid haemorrhage and 3 women with transient cerebral ischaemia; there were 2 visits for acute myocardial infarction.

Table 6: Hospital visits made by women recruited to IBIS: Diseases of the Vascular System

3 digit code	Diagnosis	Number of visits	%
454	Varicose veins	22	23.91%
413	Angina	13	14.13%
401	Hypertension	11	11.96%
427	Cardiac dysrhythmias	7	7.61%
429	Complications of heart disease	6	6.52%
453	Venous embolism/thrombosis	6	6.52%
428	Heart failure	3	3.26%
435	Transient Cerebral ischaemia	3	3.26%
410	Acute myocardial infarction	2	2.17%
443	Peripheral vascular disease	2	2.17%
448	Disease of capillaries	2	2.17%
451	Phlebitis	2	2.17%
396	Disease of aortic / mitral valve	1	1.09%
402	hypertensive heart disease	1	1.09%
414	Chronic ischaemic heart disease	1	1.09%
426	Conduction disorders	1	1.09%
430	Subarachnoid haemorrhage	1	1.09%
444	Arterial embolism	1	1.09%
447	Other disorders of arteries	1	1.09%
344	Other	1	1.09%
	Outpatient	5	5.43%
	Total	92	100.00%

Diseases of the Nervous System and Sense organs

The majority of conditions listed under diseases of the nervous system and sense organs in Table 7 below, are concerned with either visual disturbances (25%) or disorders of the eye (7.7%). 19 women experienced visual disturbance requiring a visit to an ophthalmologist. Other conditions included here are 5 visits by 4 women for epilepsy (345) and 8 women with 9 visits for vertigo (386).

Table 7: Hospital visits made by women recruited to IBIS: Diseases of the Nervous System and Sense Organs.

3 digit code	Diagnosis	Number of visits	%
368	Visual disturbances	19	24.68%
386	Vertigo	8	10.39%
375	Lacrimal disorders	6	7.79%
345	Epilepsy	5	6.49%
361	Retinal detachment	4	5.19%
365	Glaucoma	4	5.19%
369	Low vision	3	3.90%
389	deafness	3	3.90%
Other diagnosis		23	29.87%
Undefined		2	2.60%
Total		77	100.00%

Diseases of the Endocrine and Metabolic System

Endocrine, nutritional metabolic diseases and immunity disorders are shown in Table 8. Diabetes accounts for a large proportion of the visits in this group (9 women with 12 visits) with thyroid disorders in general being the most frequent. 11 women in this group made 13 visits for mineral disorders. There were 4 visits for disorders of the immune system, 7 for ovarian dysfunction and 3 for thyrotoxicosis.

Table 8: Diseases of the Endocrine, Metabolic and Immune System

3 digit code	Diagnosis	Numbers of visits	%
246	Thyroid disorders	18	24.32%
250	Diabetes mellitus	12	16.22%
275	Mineral disorders	13	17.57%
256	Ovarian dysfunction	7	9.46%

279	Immune disorders	4	5.41%
242	Thyrotoxicosis	3	4.05%
244	Hypothyroidism	3	4.05%
272	Disorders of lipid metabolism	3	4.05%
240	Simple goitre	2	2.70%
252	Parathyroid disorders	2	2.70%
253	Disorders of pituitary	2	2.70%
251	Pancreatic disorders	1	1.35%
266	Vitamin B deficiency	1	1.35%
271	Carbohydrate transport disorder	1	1.35%
274	Gout	1	1.35%
276	Fluid imbalance	1	1.35%
	Total	74	100.00%

Procedures undertaken during visits to hospital by women recruited to IBIS

There were 507 hospital visits where an HRG was reported out of 1321 total visits reported (see Table 9). The proportion of HRGs reported at each of the IBIS follow up visits is around 8% on each of the visits apart from at 6 months where it is only slightly lower at 6.7%. Overall there is no indication of an increase in the rate of hospital use requiring a procedure by women in IBIS with increasing time on the trial.

Table 9: Number and proportion of hospital visits including a procedure assigned to an HRG and % of all follow up visits including a procedure. (Ordinary outpatient visits defined as those without procedures undertaken.)

Month	MONTH06	MONTH12	MONTH18	MONTH24	MONTH30	MONTH36	MONTH42	MONTH48	Grand Total
HRG	132	123	96	65	39	24	18	10	507
Out patient	221	166	148	103	90	50	21	11	810
not known	2	1	1	0	0	0	0	0	4
Total	355	290	245	168	129	74	39	21	1321
All IBIS visits	1966	1545	1160	851	480	262	110	21	6395
% HRG	6.7%	7.96%	8.27%	7.63%	8.12%	9.16%	na	na	7.92%

The numbers and causes of hospital procedures, which are assigned an HRG reported by women in the study, are shown in Table 10. The HRGs are given for all major or minor causes of hospital admission and day cases; breast biopsy and other diagnostic procedures such as those for investigation of the digestive system are included.

Table 10: Women recruited to IBIS undergoing Procedures (assigned to Health Care Resource Groups - HRGs) during hospital visits.

Hospital visits made by women in IBIS by procedure and		
Health care Resource Groups (HRGs).		
HRG	**Procedures**	**Number**
	Ophthalmic procedures	
b04	operation on eyelid	1
b05	corneal graft	1
b06	cataract	2
b07	detached retina, vitreous detachment and tear duct operation	3
	Cancer	
BRCA	breast cancer	18
CABLA	bladder cancer	1
CACOL	colon cancer	1
OVCA	ovarian cancer	2
d02	lobectomy (lung cancer)	1
	Ear, nose and throat procedures	
c04	wisdom tooth extraction	5
c22&c32	surgery to nasal passages & sinus operations	4
c24	mouth or throat procedures including throat biopsy and treatment for vocal cords	5
c34	operation on salivary gland	1
	Respiratory	
p04	pneumonia	9
d07	bronchoscopy	1
d14	atypical viral pneumonia	1
d22	asthma	3
	Vascular	
e12	acute myocardial infarction	2
e21	deep vein thrombosis	7
a06	subarachnoid haemorrhage	1
q11	varicose veins	19
	Digestive system	
f16&f35	endoscopy or sigmoidoscopy	34
f12	surgery to stomach or duodenum(very major)	1
f32	surgery to large intestine (very major)	1
f47	other general abdominal disorders	3
f65	gastrointestinal bleed	1
f71	abdominal hernia(w cc)	1
f82	appendectomy	5
f95	haemorrhoidectomy	4
	Liver or biliary	
g05	liver biopsy	1
g08	polycystic disease	1
g12	cholecystectomy	11

g15	residual gallstones	1
	Musculoskeletal	
h02	primary hip replacement	2
h04	primary knee replacement	4
h07	shoulder, ankle or elbow replacement	2
h09	ant cruciate ligament reconstruction	1
h10	arthroscopy	7
h11&h12	foot operations, amputation of toe	11
h13&h14	operations for carpal tunnel syndrome and other hand procedures	7
h17	soft tissue or other bone procedures	1
h22	musculoskeletal (minor) procedures	1
h26	Inflammatory spine joint or connective tissue	1
h37	fractures of ankle heel or other lower limb	5
h40	shoulder, elbow, wrist and other upper limb fractures	13
h44	Major cranial visceral or blood vessel injury	1
h52	removal of fixation device	1
r01	minor spinal procedures	1
r02	surgery for degenerative spinal disorders	4
r04	vertebral column injury w decompression or fluid	1
	Breast and skin care	
j02&j03	major breast surgery inc. plastics	9
j05&j07	minor and intermediate breast surgery including breast biopsy, fna, cyst aspiration and removal of lump breast surgery	71
j37	minor skin procedures	9
j39	major dermatological	1
j42	major skin infections	1
j43	major skin tumours	11
j44	benign tumours or dermatological conditions	3
	Thyroidectomy	
k01	partial thyroidectomy	1
k02	thyroidectomy	1
k08	fluid or electrolyte disorders	1
	Kidney or urinary tract infection	
l10	kidney infection	1
l19	bladders tones and bladder polypectomy	3
l23	bladder or urinary mechanical problems	3
l26	bladder neck procedure	1
l30	endoscopy(bladder)	1
l53	renal stones and renal colic	4
l54	intravenous pyelogram	1
	Genital tract	
m01&mo2&mo3	colposcopy, plus vault smear, D&C	30
m05	hysteroscopy	70
m06	sterilisation	7
m07	hysterectomy	49
	Other	
n12	pregnancy	2

q07	surgery for Raynauds syndrome	1
q10	procedures on the lymphatic system	1
a25	transverse myelitis	1
a30	epilepsy	1
s04	coagulation disorders	1
s13	pyrexia of unknown origin	1
s14	other viral illness	2
s16	poisoning or overdose	2
s25	other admissions	1
t07	depression w/o section	1
Total (HRGs)		**507**
O	outpatient	**814**
Grand Total		**1321**

The 2 most frequent reasons for admission to hospital among women experiencing a hospital visit were either minor or intermediate gynaecological procedures, principally m05 - hysteroscopy or j07 - breast interventions such as breast biopsy, fine needle aspiration of suspicious breast lump , removal of benign lump or cyst aspiration. The gynaecological procedures shown in the table as m05 (hysteroscopy or other minor procedures in the upper genital tract), m07 (hysterectomy and other more major procedures in the upper genital tract) and m03 (procedures such as D&C or colposcopy in the lower genital tract together account for over a quarter of all procedures. Including m01and m02 (minor and intermediate procedures in the lower genital tract), gynaecological procedures are a third of all procedures experienced by this group of women.

Of breast care excluding breast cancer, which is discussed separately below, procedures included under j07 together with j05 (minor and intermediate breast surgery account for some 13% of all procedures. Major breast procedures - principally prophylactic mastectomy - account for only an additional 2% of the cases. None of the women undergoing procedures in these categories had a diagnosis of breast cancer, most were classified under Disease Chapter 10 for disorders of the genital tract including 'other disorders of the breast'. The reason for prophylactic mastectomy was in most cases given as due to concern about family history from breast or ovarian cancer though in one case cancer phobia was the stated reason.

There were 18 breast cancer cases identified in this group of women. None have been assigned to an HRG since women leave the study once a breast cancer diagnosis has been made; no treatment details are available. An average cost for the treatment of breast cancer of £6000 has been assigned to these cases. Other cases of cancer identified in this group of women are one case each of gastric cancer, cancer of the colon, lung, bladder and 2 cases of cancer of the ovary. HRGs were assigned to 2 of these cases since the women remained in the study. These were d02 for lobectomy of the lung and f12, for major gastric surgery.

Eleven women have a procedure code for skin tumours (j43). This includes 2 women with malignant melanoma and 9 with other skin neoplasms such as rodent ulcer or basal cell carcinoma; a further 2 women had benign tumours removed (j44).

Admissions to hospital for disorders of the digestive system are also common in this group. Most (f16 and f35) are for endoscopy or colonoscopy (including sigmoidoscopy). A small proportion of women had haemorrhoidectomy and 2 cases of major surgery either of the stomach or large intestine (including the case of gastric cancer described above.

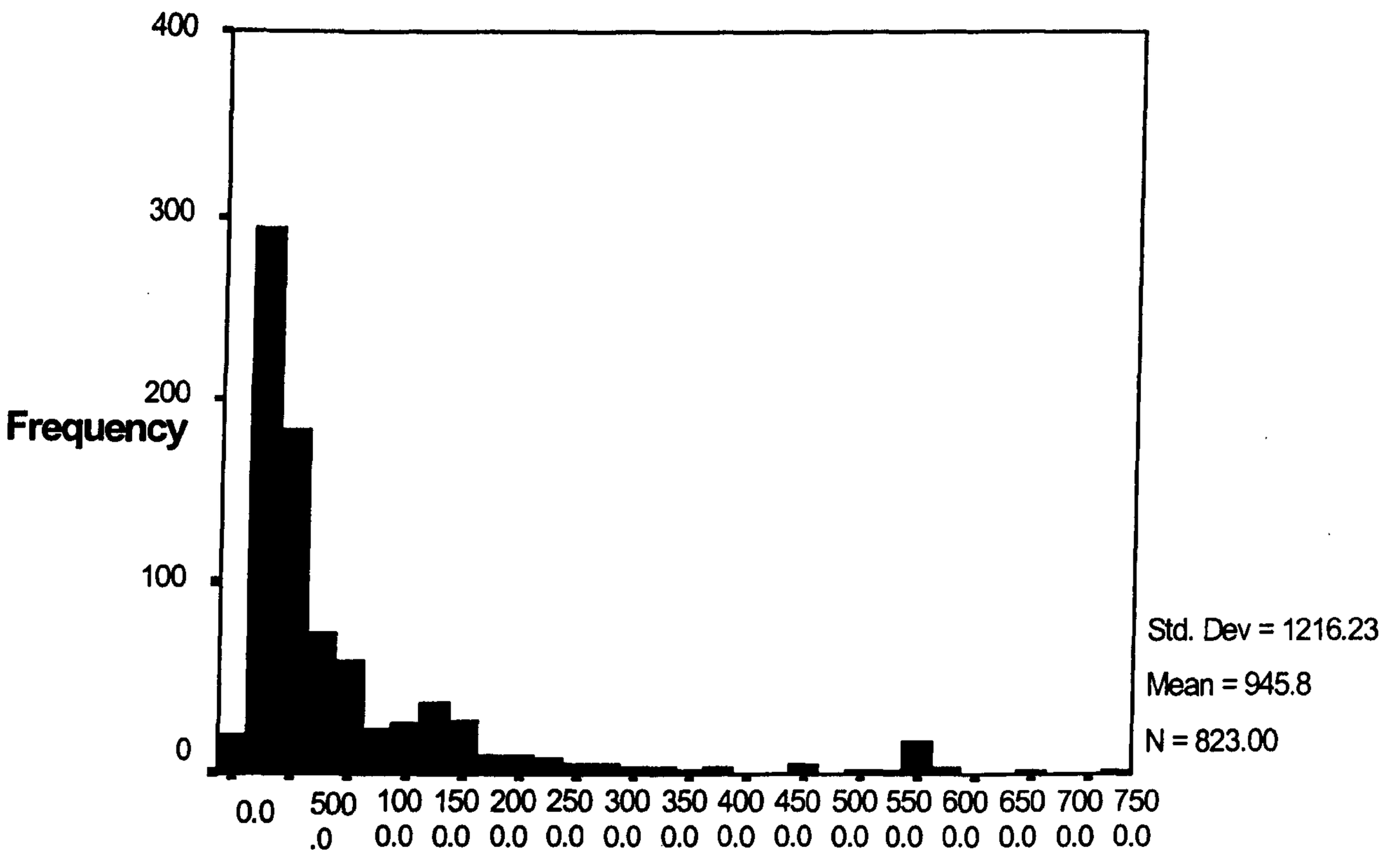
Any impact of tamoxifen on osteoporosis or musculoskeletal system in general is likely to be slow to progress. There were only 18 fractures requiring a hospital procedure recorded among this group of women, these were mainly in the wrist or other upper limb region (shoulder and elbow) with only 5 fractures in the ankle or lower limb. A small number of 11 women experienced orthopaedic operations due to arthritis mainly foot operations with 4 for carpal tunnel syndrome. There were 7 arthroscopies.

Other than the cancer cases described above, very few procedures of concern to women taking tamoxifen have been recorded in those reporting hospital visits. There have been 7 reports of thrombosis (pulmonary embolism or deep vein thrombosis) and no reports of endometrial cancer in this group. 7 women reported hospital procedures involving ophthalmic problems: problems of detached retina and vitreous humour, cataract, corneal graft and an operation on an eyelid. Visual disturbances, in general, are more likely to be seen as outpatients.

Distribution of cost

A frequency distribution of the total costs including all ordinary outpatient visits and those assigned an HRG is shown below.

Fig 2. Frequency distribution of the cost of hospital visits per woman recruited to IBIS.

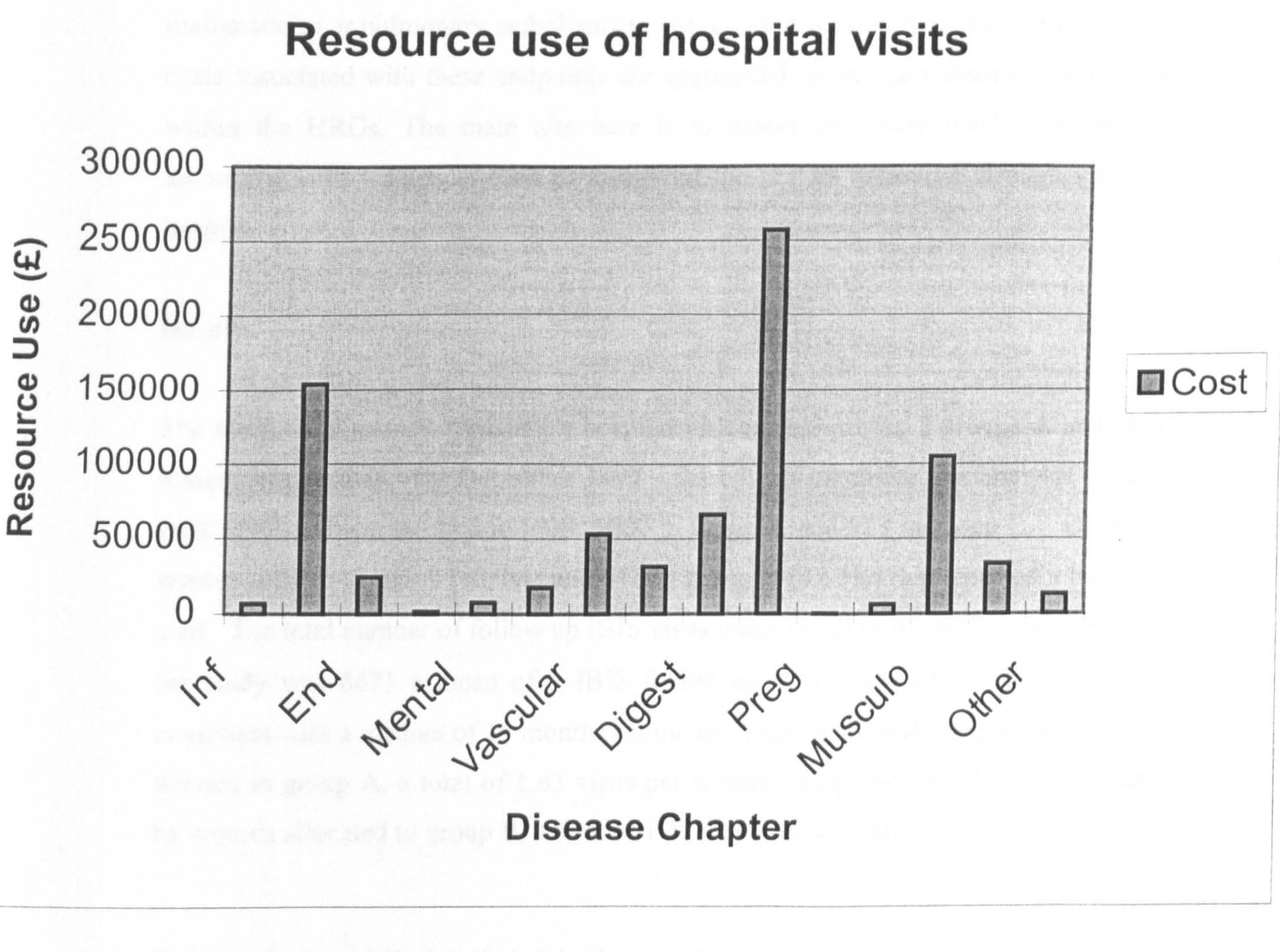


Of women reporting a hospital visit the mean cost per hospital visit is £945.80. The median cost of hospital visits for all women reporting a visit is less at £507 suggesting that most of the resource use is in the early part of the distribution. Although only the reported visits are shown in the histogram, the total distribution of costs of hospital visits for all women recruited to IBIS is in fact non normal having a long left hand tail

since most women (over 60%) have not had a visit to hospital. The range of costs for those reporting a hospital visit is £74 - £7793 for 823 women.

Figure 3. shows how the total resource use on hospital visits by women in IBIS is distributed among the major ICD9 Disease Chapters.

Fig 3: Costs of visits to hospital by women in IBIS by main ICD9 disease chapter.



In line with the distribution of numbers of visits the greatest costs are seen in the disease chapter concerned with gynaecological and breast symptoms. The second major category of costs is however in the group containing malignancies. Visits concerned with musculoskeletal disease account for the next largest category of cost followed by diseases of the digestive system including biliary disease and diseases of the vascular system.

Differences in the pattern of hospital visits for women taking tamoxifen or placebo

Method of Analysis

The data were separated into tables comprising women taking tamoxifen or placebo. The two groups are labelled A and B though may not represent the same arm of the trial throughout the analysis. Adverse disease end points and such as serious malignancies or pulmonary embolism are not reported separately in the 2 groups. The costs associated with these endpoints are aggregated under main disease headings or within the HRGs. The main aim here is to assess the likely level of morbidity associated with women in each of 2 arms of the trial as measured through visits to hospital.

Results

The number of women reporting a hospital visit in each of the 2 groups A and B is remarkably similar. By December 1997 - the cut off taken for this analysis - there were 1988 women enrolled in IBIS, 1000 in group A and 988 in group B. Of these women, 407 in group A (40.7%) and 418 in group B (42.3%) had reported a hospital visit. The total number of follow up IBIS visits made by all of the women recruited to the study was 6471 a mean of 3 IBIS follow up visits for each women recruited consistent with a median of 18 months follow up. There were 664 visits to hospital by women in group A, a total of 1.63 visits per woman compared with 657 visits made by women allocated to group B, a total of 1.57 visits per woman.

Reasons for hospital visits by main disease chapter

The rate of reporting of hospital visits is the same in each of the two groups A and B as for all women. In Table 11, the ranking of the disease chapters in terms of the number and proportion of total visits in each series is similar in both series to that seen in the total of hospital visits presented earlier.

Table 11: Number and % of Hospital visits made by women in either A or B by main ICD 9 Disease Chapter.

Disease Chapter In order of%	*Series A*	*% of Total in Series A*	*Disease Chapter In order of Series A*	*Series B*	*% of Total in in Series B*
Genitourinary	226	32.90%	Genitourinary	203	32.02%
Musculoskeletal	114	16.59%	Musculoskeletal	81	12.78%
Digestive	62	9.02%	Digestive	75	11.83%
Vascular	47	6.84%	Vascular	45	7.10%
Endocrine and metabolic	38	5.53%	Endocrine	36	5.68%
Respiratory system	33	4.80%	Respiratory	24	3.79%
Nervous/sense organs	32	4.66%	Nervous system	45	7.10%
Neoplasm	32	4.66%	Neoplasms	29	4.57%
Injury and poisoning	29	4.22%	Injury	32	5.05%
Skin	13	1.89%	Skin	18	2.84%
Infectious disease	12	1.75%	Infectious	5	0.79%
Mental disorders	9	1.31%	Mental	5	0.79%
Pregnancy	3	0.44%	Pregnancy	0	0.00%
Blood	2	0.29%	Blood	3	0.47%
Unassigned	35	5.09%	Unassigned	33	5.21%
Total	**687**	**100.00%**	**Total**	**634**	**100.00%**

Most women attended hospital for reasons associated with principally Disease Chapters 10, 13, 9 and 7: diseases of the genitourinary system (both breast diseases and reasons associated with the genital organs such as menstrual disorders), musculoskeletal disorders, digestive and cardiovascular problems respectively.

There are no obvious differences in the rate of hospital use between the 2 series of women (Table 12). For the most part the width of the 95% confidence intervals for the odds ratio between the 2 series reflects the small sample size for most of the disease categories. There may be a statistical association in the rate of visits for vascular causes between series A and B with an odds ratio of 1.06 (CI: 1.04-1.07). For neoplasms the odds ratio is1.12 (CI: 1.06-1.1). In the largest category - that of genitourinary diseases - the odds ratio is 1.13 but the confidence interval includes 1.0 suggesting that the result is not significant for p=0.05. Likewise for musculoskeletal conditions the odds ratio suggests an effect though the confidence interval is wide and includes the null value suggesting that there is no statistical significance at this level.

Overall the odds ratio of 1.1 between series A and B for all hospital visits also has a confidence interval that includes 1.0 (CI: 1.00-1.21).

Table 12: Hospital Visits for Series A and B in each main Disease Chapter

Disease chapter	Total (A&B)	Total (A)	Total (B)	Odds ratio	Confidence interval (95%)
Genitourinary	429	226	203	1.13	1.0 - 1.29
Musculoskeletal	195	114	81	1.43	0.59 - 3.44*
Digestive	137	62	75	0.84	0.69 - 1.01
Vascular	92	47	45	1.06	1.04 - 1.07
Endocrine and metabolic	74	38	36	1.07	1.05 - 1.09
Respiratory system	57	33	24	1.39	0.89 - 2.19
Nervous system and sense organs	77	32	45	0.72	0.44 - 1.19
Neoplasm	61	32	29	1.12	1.06 - 1.18
Injury and poisoning	61	29	32	0.92	0.89 - .95
Skin	31	13	18	0.73	0.54 - 0.98
Infectious disease	17	12	5	2.43	0.44-13.54
Mental disorders	14	9	5	1.83	0.87-3.82
Other	8	5	3		
Unassigned	68	35	33	1.08	1.05-1.10
Grand Total	1321	687	634	1.1	1.00-1.21
****significant(p<0.05)***					

Procedures undertaken by women taking tamoxifen or placebo during hospital visits.

Table 13 shows the differences between the 2 series in use of all of the procedures categorised as HRGs. The list contains only those procedures where visits occur in sufficient numbers to allow meaningful analysis and for conditions or disease areas, which might be affected by tamoxifen. Conditions such as multiple sclerosis, asthma and eczema are not included in this part of the analysis since they occur in this series in extremely small numbers and there is no evidence that they are affected by tamoxifen.

The following analysis includes HRGs in main ICD9 Disease Chapter :

- 10: including 2 main categories of procedures for either breast disease or the female genital tract. These are j02 & j03 covering major breast surgery including plastics, j05 & j07 covering minor and intermediate breast surgery including breast biopsy, fine needle aspiration, cyst aspiration and surgery for removal of lump and m01, m02, m03 covering colposcopy, vault smear and D&C or m05 for hysteroscopy, m06 for sterilisation or m07 for hysterectomy
- 13: principally separating the fractures which are all included in this disease chapter (both of lower limb(h37) and upper limb(h40)) from other procedures mostly associated with arthritis including h02 (primary hip replacement), h04 (primary knee replacement), h07 (shoulder, ankle or elbow replacement), arthroscopy (h10), operations for carpal tunnel syndrome and other hand procedures (h13 and h14) and h52 (removal of fixation device) following hip replacement
- 9: there are 2 main categories covering either the digestive tract or biliary conditions. The former include the diagnostic procedures of endoscopy & sigmoidoscopy (f16&f35), surgery to stomach or duodenum (f12) surgery to large intestine (f32), other general abdominal disorders (f47), gastrointestinal bleed (f65), abdominal hernia (f71) appendectomy (f82), haemorrhoidectomy (f95). Biliary conditions in this chapter include g05 (liver biopsy), g08 (polycystic disease), g12 (cholecystectomy) and g15 (gallstones)
- 7; vascular conditions have been grouped. These include: acute myocardial infarction (e12), deep vein thrombosis (e21), subarachnoid haemorrhage (a06) and varicose veins (q11)
- 6; ocular conditions have also been grouped. These include bo7 (detached retina (vitreous detachment and tear duct operation), b04 (operation on eyelid) b05 (corneal graft), b06(cataract).

The major disease chapter responsible for the largest numbers of procedures in both groups of women is for genitourinary disorders (See Table 13). This disease chapter includes procedures for genitourinary conditions concerned with breast disease and with the genital tract as listed in the bullet points above.

Table 13: Numbers of Procedures (HRGs) in the most frequent disease areas for women taking tamoxifen or placebo (Groups)

		Groups			
		A	B	OR	CI (95%)
Musculoskeletal					
	Fractures	10	12	0.85	0.79-0.91
	Other	19	20	0.96	0.96-0.97
	Total	29	32	0.92	0.89-0.95
Genitourinary					
	Breast	49	31	1.6	0.56-4.59
	Genital	85	63	1.37	0.74-2.53
	Total	134	94	1.45	0.53-3.93
Circulatory					
	Vascular	15	14	1.09	1.06-1.11
Digestive					
	Biliary	9	5	1.83	0.87-3.82
	Renal	2	9	0.23	0.01-7.37
	Other	25	23	1.1	1.06-1.14
	Total	36	37	0.93	0.91-0.95
Ocular		5	3	2.54	0.76-8.46

The odds ratio between groups A and B is indicative of a difference between the two groups for diseases of the breast and genitourinary system though the result is not significant. The confidence intervals are wide and include 1.0. This result does merit follow up in a larger series of women. Renal procedures do also show apparent excess in 1 group over the other although the numbers are small and the difference is not significant ($p<0.05$). For other main procedures there are no significant differences in the observed numbers of procedures for women in each of the two series.

Cost

There is no significant difference ($p=0.241$) between the overall cost in series A and B (see Table 14).

Table 14: Mean, median and range of costs for all hospital visits in series A and B.

Mean Median and range of overall cost for women in series A and B							
£	series A		series B				
mean	990		890				
median	553		451				
range	74-6374		1-7793				
n	418		407				
sum	413,892		362,612				

The mean total cost of visits in series A is £990 (standard error, £61.41) and median is £553 . The mean in series B is slightly lower at £890 (standard error, £61.41) and the median is £451. The histograms in fig 4 and fig 5 present the distribution of cost for all hospital visits in each of the 2 series A and B.

Distribution of resource use

Looking at the cumulative distribution of cost for each of the 2 series A and B it seems that a large proportion of the total cost of hospital visits is accounted for by a small number of women.

Figure 4: **Cumulative distribution of resource use by women in series *A***

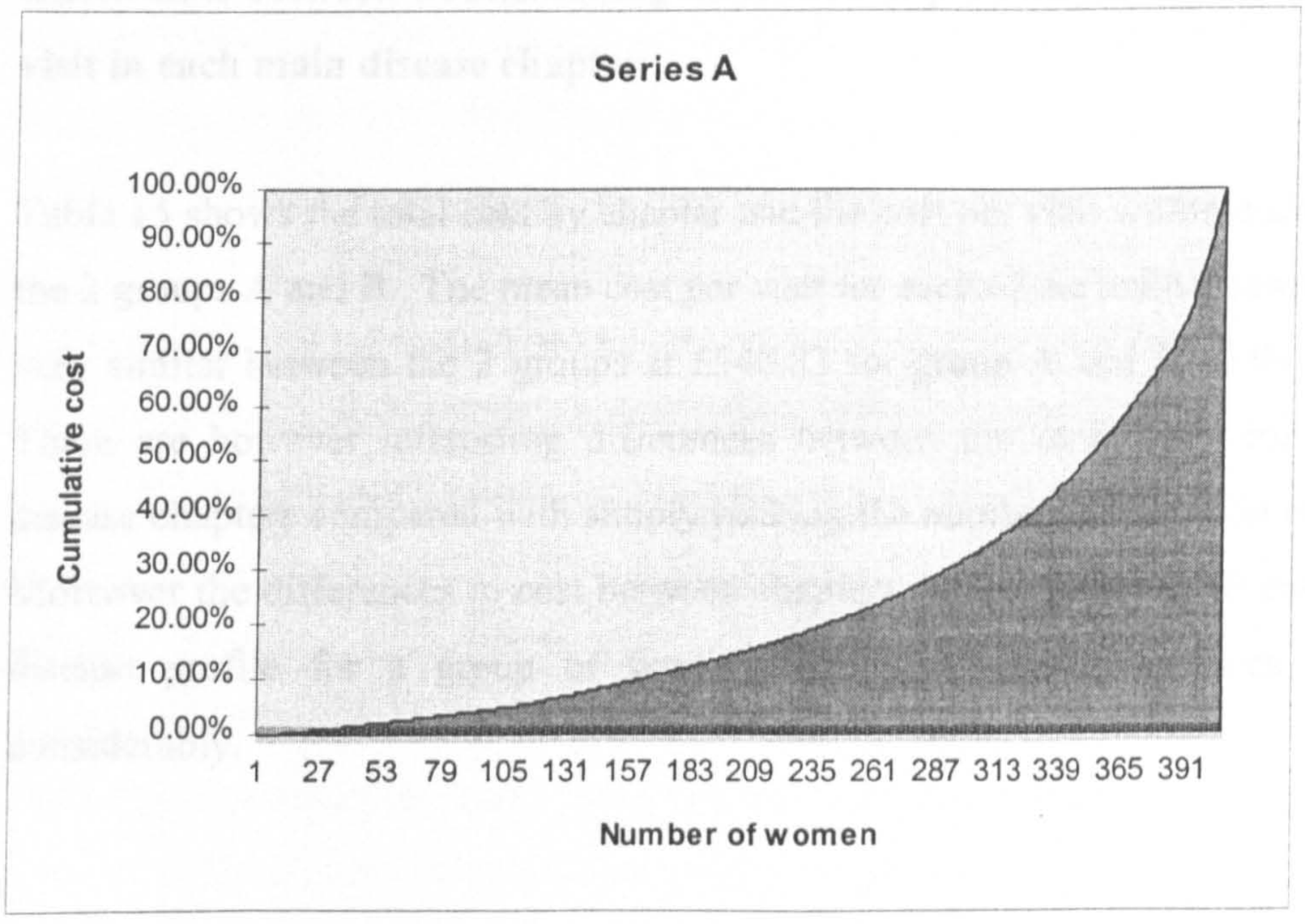
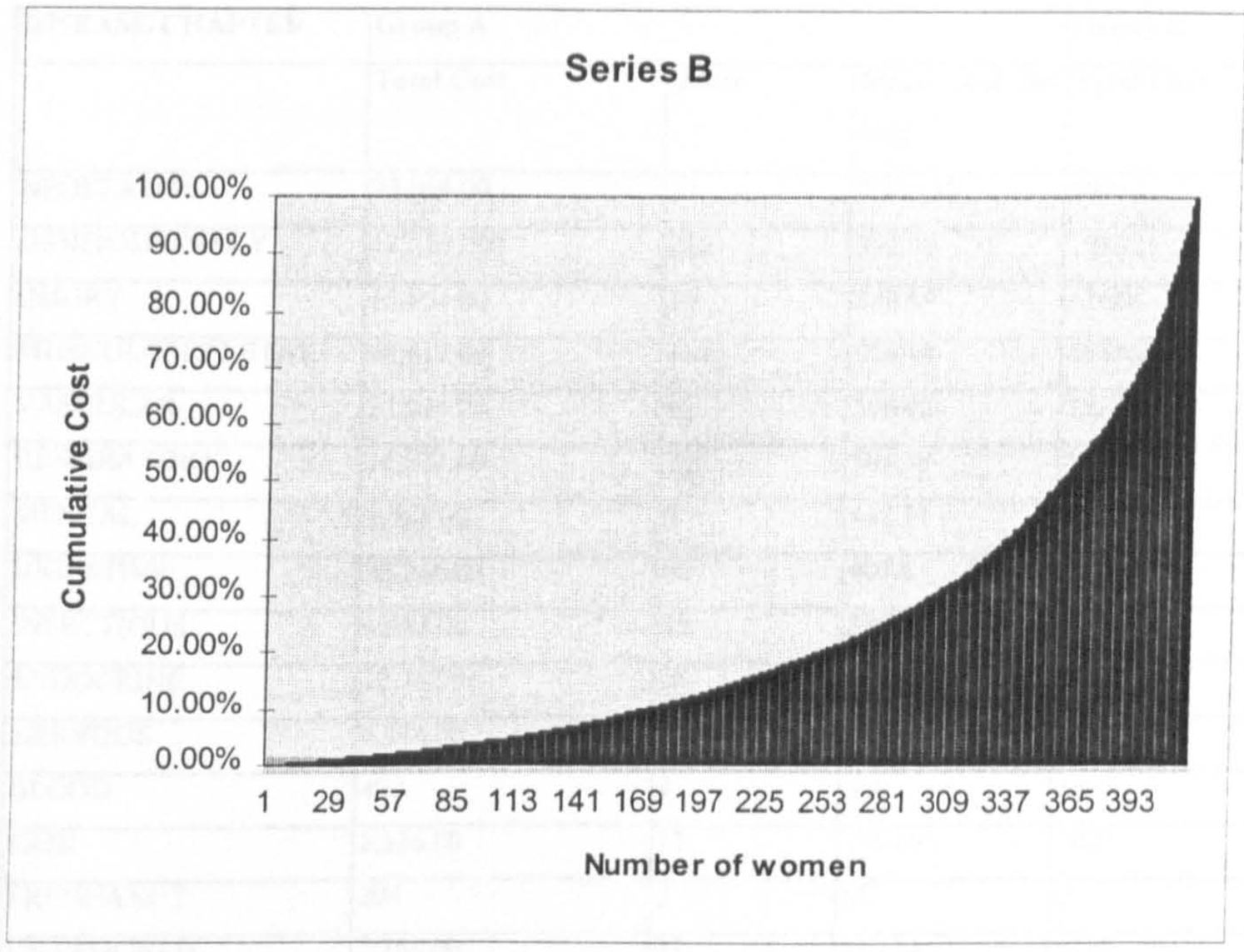


Figure 5. Cumulative resource use distribution for all hospital visits by women in series B.



The lower part of the distribution in series A shows that 203 women (50%) account for only 15% of the total cost (£53,369). By contrast, at the other end of the distribution, 11 women (3%) account for 15% of the cost.

Differences between women taking tamoxifen or placebo for the cost per hospital visit in each main disease chapter

Table 15 shows the total cost by chapter and the cost per visit within each chapter for the 2 groups A and B. The mean cost per visit for each of the main disease chapters is very similar between the 2 groups at £540.82 for group A and £540.94 in group B. There are however interesting differences between the rank order for cost across disease chapters compared with simply ranking the numbers of visits in each chapter. Moreover the differences in cost between chapters indicates that small changes in the disease profile for a group of women may affect health services costs quite considerably.

Table 15: Cost per hospital visit within each disease chapter for women taking tamoxifen or placebo (groups)

DISEASE CHAPTER	Group A			Group B		
	Total Cost	Visits	Mean cost per visit	Total Cost	Visits	Mean cost per visit
NEOPLASMS	93,964.00	32	2,936.38	59950	29	2,067.24
GENITOURINARY	127,107.00	226	562.42	128223	203	631.64
INJURY	15,854.00	29	546.69	17688	32	552.75
MUSCULOSKELETAL	58,617.00	114	514.18	46476	81	573.78
VASCULAR	23,924.00	47	509.02	29270	45	650.44
RESPIRATORY	16,612.00	33	503.39	15141	24	630.88
MENTAL	3,988.00	9	443.11	3452	5	690.4
DIGESTIVE	25,240.00	62	407.1	40929	75	545.72
INFECTIOUS	4,633.00	12	386.08	2096	5	419.2
ENDOCRINE	12,742.00	38	335.32	11560	36	321.11
NERVOUS	6,744.00	32	210.75	10853	45	241.18
BLOOD	400	2	200	1215	3	405
SKIN	2,336.00	13	179.69	3802	18	211.22
PREGNANCY	204	3	68	0	0	-
UNASSIGNED	7,756.00	25	310.24	5728	33	173.58
MEAN			**540.82**			**540.94**
MEDIAN			**407.1**			**545.72**

The table shows clearly how the costs of neoplasms is considerable; this chapter has by far the highest cost per visit despite a relatively low number of cases. Most of the women presenting with a malignant neoplasm left the study and so the costs in this category cover the total cost of care whereas costs in other categories of disease are restricted to specific procedures recorded during the visit.

The high costs of other categories of disease such as injury and poisoning and mental disorders are also apparent in the order of costs. The mean cost per patient for injury makes this the third highest cost category after the cost per patient for genitourinary disorders - the most frequent reason for attending hospital. In group B the cost per patient for mental disorders is also relatively high at £630.88 compared with an average of £540.9 overall. The difference is not significant ($p<0.05$). The cost per patient for vascular conditions is high in group B (£650.44 per visit) suggesting that the case mix is more complex compared with group A (£509.02 per visit) despite

there being a similar number of patients in the 2 groups: 47 in group A and 45 in group B.

The costs per patient are lowest in those specialities where patients are most likely to be seen in the outpatient setting. These include endocrine, metabolic or immunity disorders in ICD9 Chapter 3 with a mean cost per patient of £335.32 in group A and £321.11 in group B. This chapter includes diabetes. Diseases of the blood in chapter 4 with a mean cost of £200 per patient in group A and £405 in group B includes common conditions such as atrial fibrillation which is treated through anticoagulation clinics usually in outpatient settings. For diseases of the sense organs in chapter 6 the mean cost per patient is £210.75 in group A and £241.18 in group B. This includes routine visits for eye conditions and diseases of the central nervous system such as epilepsy also treated in outpatient settings.

The cost per patient for genitourinary conditions is higher in group B than in group A with a higher overall cost despite a smaller number of patients in this group. The series clearly includes patients having a greater severity of disease requiring more costly intervention.

Cost of main procedure (assigned to an HRG) undertaken during hospital visits for women taking tamoxifen or placebo.

Table 16 sets out the costs per HRG for the most frequent procedures undertaken during hospital visits. Costs are similar for women in the two arms of the trial. However in reviewing specific procedures it seems that the costs involved per procedure can vary within disease areas. Fractures, for example, are clearly a smaller part of the overall cost of musculoskeletal disorders than other conditions grouped under this heading. This difference is more apparent in group B.

Case mix differences between the series are also clear. Procedures concerned with the breast and genital organs for example, though more frequent in A have a higher cost per case than found in those in B.

Table 16: Cost per HRG for women taking tamoxifen or placebo (groups)

	Group A			
Main HRGs	**Nos. of HRGs**	**Cost of HRGs**	**% of total cost in group A**	**Mean cost per procedure**
Genital organs	85	82305	53.00%	968.29
Breast	49	31867	55.00%	650.35
Musculoskeletal	19	24030	41.00%	1264.74
Digestive	25	17321	66.00%	692.84
Biliary	9	12253	68.00%	1361.44
Vascular	15	11910	44.00%	794
Fractures	10	10990	56.00%	1099
Ocular	5	4863	76.00%	972.6
Renal	2	400	11.00%	200
Total	219	195939		
Mean Cost per HRG				889.25
	Group B			
Main HRGs	**Nos. of HRGs**	**Cost of HRGs**	**%of total cost in series B**	**Mean cost per procedure**
Genital organs	63	73979	47.00%	1174.27
Musculoskeletal	20	34570	59.00%	1728.5
Breast	31	25642	45.00%	827.16
Vascular	14	15173	56.00%	1083.79
Digestive	23	8865	34.00%	385.43
Fractures	12	8508	44.00%	709
Biliary	5	5702	32.00%	1140.4
Renal	9	3051	89.00%	339
Ocular	2	1550	24.00%	775
Total	179	177040		
Mean Cost per HRG				906.95

Discussion

Comparison of the rate of hospital use by the women in IBIS with routine information from the NHS admissions data supports the validity of the information collected here since the rate of hospital use is broadly that which might be expected for women in the age group. Moreover the reasons for hospital visits are similarly distributed amongst disease groups within the IBIS women and the NHS admissions data.

Comparing the rate of admission to hospital (for both ordinary admissions and day cases) for women in the general population in England (aged 45-64) [161] with the use of

hospital services by women recruited into IBIS for specific causes, does however seem to suggest a higher consultation rate for genitourinary conditions among women recruited to IBIS. Further investigation of this estimate would require more detailed information from NHS routine sources than is generally available and it is important to note that the IBIS data set is not strictly comparable with routine data collected from the NHS returns. This is because the NHS data set counts consultant episodes rather than individual women and because of the eligibility criteria for IBIS that excludes women who are likely to have a high rate of illness [168]. In particular women with a history of neoplasm or some vascular conditions such as deep vein thrombosis are ineligible for recruitment to the trial. This finding does however merit further review once recruitment is completed and analysis of hospital visits can be completed on a larger sample over a longer time period.

The pattern of reported morbidity in terms of the kinds of conditions presented is consistent with that seen in the NHS hospital admissions data with the exception of the rate of admissions for neoplasms - the commonest reason for admission in the NHS for women in this age group. Women recruited to IBIS are most likely to use hospital services for conditions associated with the breast or due to genital disorders such as fibroids or abnormal bleeding. Other frequent causes of hospital use are for musculoskeletal disorders, digestive disease and vascular disease. These causes of admission are seen in the same rank order for women in IBIS and in the NHS data set for the general population.

There are few differences in overall reported hospital morbidity for women in the 2 arms of the trial in terms of the numbers of visits for all causes. There do however appear to be some differences emerging for women in the two groups for disease associated with the breast and for genital conditions. This finding does indicate the need for further study in this area. In particular it will be important to discern - once the trial is completed - whether the difference between the 2 groups is an increase in the frequency of symptoms in these 2 disease areas for women taking tamoxifen or whether it is a protective effect.

Looking at the analysis of procedures undertaken during hospital visits (assigned to an HRG) it is apparent that small differences in cost may have a large impact overall

considering the potentially large numbers of women who might wish to be involved in taking tamoxifen prophylaxis. For breast symptoms, for example the difference in the cost per visit per HRG for women taking tamoxifen or placebo is £177 per woman with an odds ratio of 1.6 for women undergoing a procedure for breast symptoms between the two groups. Should this represent a saving on the cost of benign breast disease to the health service for women taking tamoxifen prophylaxis the impact may be substantial.

By contrast, an increase in the numbers of procedures needed to treat a possible increase in gynaecological symptoms in the intervention group by say one third of women - the difference seen between group A and B here - with the cost difference between the 2 groups of around £200 as found between A and B may give rise to a net cost of health care due to women taking tamoxifen prophylaxis. The direction of the effect found in breast and gynaecological procedures is unknown at this stage but the possible impact on the cost effectiveness of chemoprophylaxis will be tested in the sensitivity analysis presented in the subsequent chapter.

The distribution of cost for women in each of the 2 arms of the trial show that a high proportion of overall cost of hospital visits is due to a small number of women. This suggests that it is the outcome in terms of high cost adverse events particularly neoplasms which will determine the balance of cost effectiveness for tamoxifen prophylaxis of breast cancer.

The methodology used in this analysis of categorising the diagnosis into major ICD9 disease chapters is broad enough to allow comparison across major disease areas between women in the 2 arms of the trial. Costing the procedures undertaken by the women during hospital visits using HRGs takes account of possible differences in case mix between the women which may affect the costs of health care. This method of costing has been well validated within the NHS. It would not have been possible because of the small numbers involved to compare specific diagnosis between the 2 series of women or to assess in more detail the individual costs of care.

The analysis is limited at this stage because of the need for longer term follow up and the importance of retaining the blinded nature of the study. It is also important to note

that a number of biases are possible at this stage which may underestimate aspects of morbidity particularly those likely to have a lag time or latency period before symptoms develop. These will arise firstly because the period of time over which the sample was taken will underestimate longer term effects. Secondly, it is possible that women most likely to develop adverse symptomatology in relation to recruitment to the trial may have a greater tendency to withdraw than those for whom any effects of long term tamoxifen use are benign or beneficial. The nature of the randomised trial design with complete randomisation of subjects should be sufficient to address biases concerned with the latter effect though further follow up is needed to fully understand the potential for changes in morbidity of women taking long term tamoxifen on resource use associated with health services.

More detailed assessment of the hospital visits made by the women will be possible once the trial is complete and a full unrestricted analysis can take place. At this stage it appears that in general no substantial deficits or improvements in morbidity seem to occur for women recruited to IBIS or between the 2 arms of the trial. There are no differences in the pattern of morbidity in comparison with that of the general population.

Summary

The costs of changes in morbidity which might be attributable to long term use of tamoxifen is assessed through review of the use of hospital services by all women recruited to IBIS at the end of December 1997 (1988 women). Small changes in the use of hospital services or prescribed medications for the age group targeted in prevention trials could have a significant impact on overall cost if morbidity worsened or indeed improved for large numbers of the women involved. Yet, there have been few studies published on the effect of tamoxifen on morbidity as measured through changes in hospitalisation rates or use of medications. Prevention trials have published endpoints other than the incidence and mortality from breast cancer though have mostly been concerned with ischaemic heart disease and vascular events or with thromboembolism. There has been a great deal of concern about endometrial cancer.

The morbidity reported here is derived from information given by women recruited to IBIS during the first and all subsequent follow up visits. The diagnosis are recorded and assigned to an ICD 9 diagnosis code and by Health Care Resource Groups (HRGs) in order to quantify and cost them. The main value of HRGs is to provide a validated method for producing case mix adjusted information with which to compare the morbidity patterns for both arms of IBIS. No previous studies have reported the use of HRGs to describe changes in morbidity patterns in this context.

The information is aggregated to compare the numbers and reason for hospital visits looking at both diagnosis and treatment in the two arms of the trial. The approach has face validity from a comparison of the proportion of visits in each main ICD 9 grouping with the routine data available for women of the same age in the NHS hospital episode system. Although not a directly comparable data set the proportion and magnitude of women in each category is similar.

The highest proportion of visits for women recruited to IBIS were for disease of the genitourinary system (32.4%) including diseases of the female genital tract, urinary system and breast diseases followed by diseases of the musculoskeletal system (14.7%) including fractures, the digestive system (10.3%) and diseases of circulation including cardiological conditions and vascular causes (6.9%).

Of the diagnosis for genitourinary problems over 50% were for abnormalities of menstruation and abnormal bleeding resulting in procedures such as hysteroscopy or hysterectomy. An additional 20% were for breast diseases including fibroadenoma or benign breast disease and treated with fine needle aspiration or cyst aspiration. There were a number of fractures in the musculoskeletal category (18) mostly of the wrist or upper limb though most reports in this group were of back problems (21%). Procedures reported included carpal tunnel syndrome and arthropathies. Cholelithiasis was the most commonly reported diagnosis in the digestive disease category (20%). Procedures most often reported were endoscopy or colonoscopy. Among diseases of the circulatory system a large proportion of the procedures were for varicose veins (25%) with a smaller number for angina and hypertension.

Major adverse events in this series were breast cancers, and a number of other cancers including colon, lung bladder and 2 cases of cancer of the ovary. There were a number of skin tumours reported.

Separating the series into A and B according to the 2 arms of the trial, there were 407(42.3%) women reporting a hospital visit in group A and 418(40.7%) in group B. The mean costs for hospital visits were £889.25 in series A and £906.95 in series B. There were no significant differences between the 2 arms of the trial. The odds ratio for disease of the breast and genital organs does indicate a difference between the 2 groups though the confidence intervals are wide. This trend will need to be pursued further with greater accrual. Likewise some case mix differences do appear between the 2 arms of the study such that the procedures for breast disease and disorders of the female genital tract do seem to be more costly in group A than in group B. In terms of the distribution of cost a small number of women do account for a large proportion of the overall costs. This finding suggests that it will be the impact of tamoxifen chemoprophylaxis on increasing or reducing the incidence of high cost procedure that determines the cost impact from morbidity. The findings presented here suggest that there are no major differences in morbidity for women taking tamoxifen or control though the results may warrant further investigation particularly for disease of the genitourinary system. The method of quantifying the data with HRGs is a useful means of categorising and costing data of this kind.

Consequently in the model of cost effectiveness of tamoxifen chemoprophylaxis developed in Chapter 7 the baseline case does not include the cost of morbidity for women taking tamoxifen although the likely increased risk of endometrial cancer is included. In constructing the sensitivity analysis for cost effectiveness in Chapter 7 however, it did however seem reasonable to include a possible effect of long term tamoxifen use of hospital visits for benign breast disease. Further work pending continued recruitment to IBIS will clarify this issue. Including morbidity within the sensitivity analysis provides information on the impact of possible changes in morbidity within a range of estimates.

Chapter Five

Morbidity and Resource Use:

Use of Medication

Introduction

As discussed earlier, this chapter builds on information set out in Chapters 2 and 4 seeking to define a cost estimate for the likely impact of changes in morbidity of women taking tamoxifen chemoprophylaxis. In this chapter measures of morbidity are made from changes in the use of prescribed medications for women recruited to either the tamoxifen or the control arm of the International Breast Cancer Intervention Study (IBIS).

Analysis of the reported use of medications by women enrolled into IBIS provides an independent means of understanding possible morbidity of tamoxifen prophylaxis and the costs (or savings) associated with it. This section presents information on the medications taken by a series of women enrolled in IBIS during each of their routine six monthly visits over a maximum of 48 months. Only those drugs thought to interact with or be affected by tamoxifen, as discussed in Chapter 2, have been reviewed in detail. Most of the drugs included in the main analysis are available on prescription only with the exception of evening primrose oil which is purchased as an over the counter medication for the relief of breast pain and other menstrual or menopausal symptoms.

Method

The sequence of visits, for women enrolled into IBIS, to the study centres has been described earlier (Chapter 3). The information on use of medications is collected in the same way as for hospital visits. Women are asked at each six monthly visit about medications prescribed in the previous six-month period. The name of the drug and the dose are recorded on the follow up form.

This information was downloaded onto an Excel spreadsheet for all women enrolled up until the end of December 1997. The information was first reviewed to ensure completeness of data collection particularly to ensure correct labelling for drug names to avoid confusion when assigning to generic categories using the British National Formulary (BNF)[16]. Drugs unlikely to be associated with tamoxifen use were then removed from the data set. These included antibiotics, antimalarials, asthma drugs and inhalers, analgesics other than for breast pain or migraine, vitamins and food supplements such as iron, calcium and cod liver oil.

It is of course possible that the numbers of drugs taken by women in the study is a measure of their overall health and well being and that this may be affected in some general way by tamoxifen prophylaxis. It was not however considered possible to make general conclusions about this issue by studying all categories of drugs irrespective of their likely interaction with tamoxifen. Changes in use of a wide variety of different drugs would not be comparable and the small number of drugs in each of the excluded categories as well as the wide spectrum of indications for their use would make subcategorisation difficult to interpret. Antibiotics for example, are widely prescribed for a range of conditions with well-known differences in the threshold of symptomatology preceding a decision to prescribe. Changes in the use of antibiotics by women recruited to IBIS could have a variety of interpretations with no clear relevance to tamoxifen prophylaxis.

The remaining drugs, those used for the treatment of symptoms in three main systems: for cardiovascular disease, for abnormalities of the endocrine system, and for symptoms associated with the central nervous system - mostly psychiatric drugs for the treatment of depression are set out in Table 1. Drugs for migraine and the specific drug thyroxine are included separately. The numbers of women reporting taking each one of these drugs is included in the table. The two largest categories of drugs: those associated with cardiovascular or psychiatric treatment have been further subdivided. Medical advice was sought to support the assignment of drugs according to usual prescribing practice. Disaggregation only down to the level of major sub categories was favoured since local variations in prescribing practice would reduce the value of

further analysis. The drugs were then grouped by generic categories under the main headings described above.

Comparisons between the rates of use of drugs for women in IBIS with those in the general population are made using data from a single General Practice and by reference to the National Morbidity Survey[173]. Routine information on drug use by age is not collected nationally. The GP research database administered by the Department of Health contains information on GPs prescribing, but this is not routinely broken down into age categories relevant to women enrolled into IBIS. Moreover the reasons for prescribing a particular drug may overlap and indeed many different drugs are prescribed for the same condition. An example relevant to this study is the use of the beta-blocker, propranolol, which can be used either as a migraine prophylaxis or as an antihypertensive agent.

The main aim of this study was to gain an understanding of the likely differences in morbidity and costs between the two arms of IBIS as measured by differences in prescribed medicines for women taking tamoxifen and those on placebo. Also, the results could highlight areas where further study of prescribing patterns for women taking tamoxifen prophylaxis may be productive.

Once the drugs to be studied were separated from all other reported medications, tables were obtained for women in the two arms of IBIS. In the same way as for the hospital visit data, these remain anonymised pending completion of the trial. The results are set out below. A further analysis was undertaken to review differences for women who were prescribed new medications after they were recruited to IBIS.

Results

Main categories of drugs reported

Over the time period reviewed, 1279 women out of 2531 women recruited to the study during the time period (50.5%) reported having taken 3054 drugs since their last IBIS visit as discussed above. Large proportions of these drugs (79.7%) are not

included in the final analysis because they are unlikely to have any relevance in relation to tamoxifen. Table 1 below shows the remaining 687 women (27.1% of those recruited) who reported taking prescribed medications in the categories thought most likely to indicate morbidity associated with tamoxifen chemoprophylaxis. The proportion of drugs in each of main categories and the rate of use of drugs in each category by women recruited to the trial is also given.

Table 1. Self reported use of medications by women recruited to IBIS in main BNF categories.

	Main Categories of Drugs (BNF)					
	Cardiovascular	**Psychiatric**	**Endocrine**	**Migraine**	**Thyroxine**	**Total**
				(without propranolol)		
Number of women	302	174	84	48	79	687
% in category	43.9	25.3	12.2	6.9	11.5	100%
rate of use	11.9	6.87	3.32	1.89	3.1	27.1

The main categories include drugs associated with the cardiovascular system (43.9%), the endocrine system including thyroxine (11.5%) as well as drugs prescribed for breast pain and associated symptoms (12.2%), and finally the central nervous system including the psychiatric drugs (25.3%) - tricyclics and SSRIs for the treatment of depression, hypnotics - sleeping tablets - and anxiolytics, for the treatment of anxiety as well as analgesics for migraine (6.9%).

Drugs associated with the cardiovascular system

302 women report taking at least one of the drugs listed in Table 2 prescribed for cardiovascular symptoms. The numbers below each of the subheadings for cardiovascular drugs show how many drugs were reported in each category. 67 women report taking more than one drug and a small number of women (7) report taking three prescribed medications.

Table 2. Cardiovascular drugs reported by women recruited to IBIS: numbers in each subcategory. Specific drugs are also listed.

Beta Blockers	**Diuretics**	**Lipid lowering**	**Calcium Blockers**	**ACE Inhibitors**	**Glycosides**	**Alpha Blockers**	**Arrhythmia**	**Nitrates**
Atenolol	Bendrofluazide	Bezafibrate	Diltiazem	Captopril	Digoxin	Doxazosin	Flecanide	GTN
Bisoprolol	Frusemide	Cholestyramine	Lacidipine	Enalapril				Isosorbide
Metoprolol	Indapamide	Clofibrate	Nicardipine	Lisinopril				Nitrates
Oxprenolol	Spironolactone	Pravastatin	Nicorandil					
Propranolol	Triamterene	Simvasatin	Nifedipine	Perindopril				
Sotalol		Atorvastatin	Verapamil	Ramipril				
Timolol		Fluvastatin		Trandolapril				
131	109	36	52	57	2	3	2	7

Beta blockers and calcium blockers together account for the highest proportion of prescribed medications in this category (45.8% of the total drugs prescribed) and are used primarily for angina and hypertension. Diuretics, ace inhibitors and glycosides (42% of the total number of drugs), form the second largest group and are prescribed primarily for heart failure though there is increasing cross over in prescribing between these sub categories of drugs.

Lipid lowering drugs accounting for just less than 10% of the total prescribed drugs are used for secondary prevention of myocardial infarction though are being increasingly used in primary prevention for people with a high cardiovascular risk profile. Women taking more than two drugs are most likely to be hypertensive prescribed a diuretic and either a beta blocker (11 women), or a calcium blocker (13 women), or an ACE inhibitor (15 women). Other combinations (28) include beta blockers and lipid lowering drugs most likely to be given after myocardial infarction for secondary prevention or beta blockers and ace inhibitors for prevention of heart failure.

Drugs associated with the endocrine system

There were 84 women reporting use of four drugs concerned with the endocrine system taken for the treatment of breast pain and associated symptoms (see Table 3). These drugs are collectively referred to as Epos. Evening primrose oil was most commonly reported (68%). This is the only medication in the data set, which is purchased rather than prescribed. A small number of women reported taking two drugs.

Table 3. Endocrine system: Drugs reported by women recruited to IBIS for treatment of breast pain and menstrual symptoms

Drug		Number reported	
Efamast		14	
Epogam		14	
Evening Primrose Oil		61	
Efamol		1	
Total		90	

In addition, thyroxine was reported by 79 women. This drug is taken for an underactive thyroid gland causing symptoms of persistent tiredness, lethargy and weight gain.

Drugs associated with psychiatric symptoms

There were 174 women reporting taking drugs for psychiatric morbidity (see Table 4). Most are taking only one drug most likely to be an antidepressant - either Tricyclics or Selective Serotonin Re-uptake Inhibitors (SSRIs), together these account for 85% of the total. Hypnotics (sleeping tablets) and anxiolytics for anxiety are each less than 10% of the total. A small number of women are taking two drugs usually an antidepressant in the SSRI category and a hypnotic to aid sleeping.

Table 4. Psychiatric drugs: numbers reported in each subcategory. Specific drugs are also listed

Hypnotics	**Anxiolytics**	**Tricyclics**	**SSRIs**	Total
Zoplicone	Diazepam	Amitryptyline	Venflexane	
Temazepam	Buspirone	Dothiepin	Sertraline	
Nitrazepem		Nortryptyline	Paroxetine	
		Lofepramine	Fluoxetine	
		Imipramine	Paroxetine	
		Clomimpramine		
18	11	97	67	193

Analgesics and prophylaxis for migraine are set out in Table 5. The drug Propranolol is included in this table since it can be used both for the treatment of migraine or as an antihypertensive agent

Table 5. Drugs reported by women recruited to IBIS for Migraine.

Specific drug	**Number**
Propranolol	25
Pizotifen	3
Paramax	2
Migril	1
Migraleve	4
Migraine Tabs	2
Imigran	21
Ergotamine	1
Clonidine	16
Inderal	14
Total	**89**

80 women reported taking 89 drugs in this category. Omitting propranolol there were 48 women taking 51 drugs.

Differences in prescribed medication between those taking tamoxifen or placebo

The tables below are the results of separating the data for women in each of the 2 arms of IBIS. The identity of each arm remains anonymised pending the completion of the trial. The first section is concerned with all women reporting use of drugs in the series. Table 8 deals with woman reporting drugs newly prescribed subsequent to their recruitment to IBIS.

Cardiovascular drugs

The odds ratios for each of the categories of cardiovascular drugs shown in Table 6 suggest that there is no significant difference between the 2 arms of the trial for ace inhibitors or diuretics for p=0.05. For beta blockers, calcium blockers and lipid lowering drugs the confidence intervals are wide including 1.0 in each case suggesting that while there may be an effect between the two arms of the trial the sample size is too small at this stage for meaningful analysis.

Table 6. Differences in the use of Cardiovascular drugs by women taking tamoxifen or placebo (groups)

	Cardiovascular drugs (number of women)					
	Ace	Beta	Diuretics	Lipid	Calcium	Others
Groups	Inhibitors	Blockers		Lowering	Blockers	
A	27	81	57	23	22	7
B	30	50	52	13	30	7
Odds ratio	0.9	1.66	1.1	1.78	0.73	
CI	0.86-0.94	0.40-6.87	1.05-1.16	0.67-4.73	0.51-1.04	

Psychiatric drugs

Table 7 shows the drugs prescribed for anxiety and depression separated into two groups A and C corresponding to the two arms of IBIS. There may be an association

between chemoprophylaxis and use of antidepressants although the strength of the effect for SSRIs seems greater than for women on tricyclics and grouping these two categories reduces the effect. There are too few women taking hypnotics and anxiolytics to demonstrate an effect between the two arms of the trial.

Table 7. Differences in the use of drugs by women taking tamoxifen or placebo (groups)

	Psychiatric drugs			
	Tricyclics	**SSRIs**	**Hypnotic**	**Anxiolytics**
Groups				
C	50	29	7	7
D	47	37	10	3
Odds ratio	1.07	0.78	0.7	2.34
95%CI	1.05-1.09	0.61-1.00	0.54-0.91	0.8-6.9

Endocrine system

Of the 84 women reporting taking drugs in this category, 38 were in one arm of the trial and 46 in the second. The odds ratio is 0.82 (95%CI =0.69-0.98) indicating that there might be a small effect for this category of drugs.

Migraine

For the migraine drugs including propranolol the women separated into the two arms of the trial with 43 in on group and 37 in the second group. The odds ratio is 1.17 (95%CI=1.3-1.05) suggesting a small but potentially interesting difference between the two groups.

Drugs initiated while on the study

Table 8 below shows the numbers of women whose first report of a prescribed drug began on the first or subsequent follow up visits i.e. women whose report of

prescribed medications began after recruitment to the trial. These are separated into the main categories described above and to each of two groups corresponding to either the tamoxifen or placebo arm.

Table 8. Differences in reports of drugs newly prescribed subsequent to recruitment to IBIS for women on tamoxifen or placebo (groups)

Drugs initiated while on the study				
	Group			
Drugs	E	F	Odds ratio	95% CI
Migraine	10	14	0.71	0.54-0.94
Migraine (inc. Propranolol)	17	21	0.81	0.70-0.93
Epos'	30	31	0.97	0.96-0.97
Thyroxine	10	17	0.59	0.28-1.21
Cardiovascular Drugs				
Beta blockers	31	46	0.67	0.33-1.35
Lipid lowering drugs	9	18	0.5	0.15-1.68
Calcium blockers	20	23	0.87	0.81-0.93
Ace inhibitors	13	18	0.72	0.54-0.97
Others	3	7	0.43	0.15-1.25
Psychiatric drugs				
Hypnotics	4	5	0.8	0.74-0.86
Anxiolytics	2	5	0.4	0.14-1.13
Tricyclics	31	32	0.97	0.96-0.97
SSRIs	21	30	0.7	0.44-1.10

There does appear to be a difference between the two groups for migraine both where Propanolol is excluded (OR=0.71,95%CI=0.54-0.94) or included (OR=0.81, 95%CI=0.7-0.93) in the sample although both include confidence intervals approaching 1.0 suggesting that the effect is unlikely to be significant. For cardiovascular disease the odds ratio for beta blockers and lipid lowering drugs are 0.67 and 0.50 respectively though the confidence intervals are wide and in both cases include 1.0 suggesting that the effect is not significant for p=0.05.

For women taking antidepressants the main difference again appears to be a higher number of women taking SSRIs though again there are only small numbers involved and the difference is not significant. For medications in other categories more women initiated thyroxine in one arm compared with the other; the difference is not significant.

Discussion

Analysing the use of drugs by women in IBIS is limited by the quality of the data collection. A great deal of time was spent in validating the records entered into the system and establishing the identity of the drugs recorded, moreover it is difficult to assess the completeness of the data collection. In particular it was not possible to assess dose from the records since this was not recorded consistently. It is likely also that there may be some error in assignment of drugs to causes. Nevertheless it is clear that a large proportion of the drugs listed are unlikely to have any association with tamoxifen chemoprophylaxis. Only a small proportion of the drugs excluded from the analysis indicate any major illness or morbidity for women recruited to IBIS. Of those excluded the use of an anti-inflammatory drug is probably the most important category suggesting morbidity from musculoskeletal disorders primarily osteoarthritis. Other drug usage suggest relatively minor and probably self limiting illnesses such as chest infections, chronic disease such as asthma or diabetes or use of food supplements such as vitamins and minerals.

Just under a third of all women recruited to IBIS during the time period reviewed in this sample are taking - mostly - prescribed medications for morbidity which is associated with tamoxifen chemoprophylaxis. The highest proportion of drug use (43.9%) reported by almost 12% of women recruited to IBIS is for cardiovascular disease. The second largest category - psychiatric drugs accounting for just over a quarter (25.3%) of the total reported are taken at a rate of nearly 7% per women recruited to IBIS.

Coronary heart disease and mental illness particularly depression are common reasons for attendance in General Practice. There are few routine sources of information with which to compare these results. PACT data are available for monitoring prescribing in general practice though are not based on individual patients and are not published routinely. Findings from the review of activity in general practice published as Morbidity Statistics from General Practice[173] is relevant though rarely relates consultations in general practice to specific drugs. For this reason information was requested from a general practitioner[174] covering a large practice population(10,000) on the rate of use of the specific categories of drugs reported by women in IBIS. On the whole this information suggested that prescription rates are comparable for coronary heart disease though may be high for antidepressants. Over an annual period, 14.5% of women aged 45-64 in the General Practice were taking drugs for cardiovascular disease in the BNF categories described above (compared with 12% of women in IBIS) whereas only 4% were taking drugs for depression (compared with nearly 7% of women in IBIS) [181]. It is possible to speculate that women who perceive themselves to be at increased risk of breast cancer are likely to have a higher rate of use of antidepressants than the general population. Alternatively, involvement in the IBIS trial may reduce depression. There are few reports to suggest that tamoxifen itself leads to low mood although the known side effect of symptoms such as hot flushes and headaches may give rise to mood swings.

Comparing the results with the most recent findings from Morbidity Statistics from General Practice (fourth national study)[173] supports these conclusions with consultations for coronary heart disease of the order of 15% for women aged 45-64 and for depression around 7%. Since not all of these consultations would have resulted in the provision of a prescription the results are not directly comparable. They do however lend validity to the estimates given above for the overall morbidity of women in IBIS.

For specific drugs 5.6% of the General Practice population in the age group 45-64 were taking betablockers compared with 5.2% for women recruited to IBIS. Only 3.3% of women in IBIS report taking the category of drugs labelled Epos (12.2% of

the total drugs reported) for the relief of breast pain and other gynaecological symptoms. It is not possible to compare this drug directly with reports from general practice since many women take Evening Primrose Oil for the relief of gynaecological symptoms, which can be purchased over the counter. About 3% of women in IBIS report the use of thyroxine, which is similar to the rate reported in the General Practice population (3.7%). Acquired hypothyroidism is the reason for prescription of thyroxine and this was reported at a rate of 0.87% for women aged 45-64 in the Morbidity survey. Migraine was reported at a rate of 1.89% of women in IBIS compared with 1% in the General Practice population.

Differences between the two arms of the trial in the frequency of use of drugs reported here cannot be fully evaluated because of the small numbers involved. Nevertheless, there does appear to be an indication from the data of a potentially interesting difference in the two groups in the use of beta blockers. The potentially beneficial effect of tamoxifen on cardiovascular health has been discussed earlier though it is equally likely that women taking tamoxifen are prescribed betablockers to counteract vascular symptoms such as hot flushes. Since the two arms of the trial are not unblinded at this stage it is not possible to assess whether the women more likely to be taking drugs for cardiovascular disease are those randomised to the control or to the tamoxifen arm. At this stage the significance of any differences in the use of drugs for vascular symptoms in terms of cost appears to be small.

Broad cost implications might be estimated by taking the rate of use of beta blockers by women aged 45-64 in the general practice population discussed above (5.6%) and assuming that there may be a relative risk of 1.63 or 0.61 in the intervention group from IBIS data. For 1000 women assuming prescription of the drug Atenolol - a commonly used betablocker at a cost of £1/month (50mg/day) the cost for 560 women at 10 years would be £67,200. Using the assumption of an increased relative risk of 1.63 the additional cost would be £42,240 (352 women) for 10 years - around £4 per woman per year. For a reduction in relative risk of 0.62 the savings would be £26,280 (219 women) over 10 years - around £2 per woman per year.

Summary

Analysis of the medications taken by women enrolled into IBIS is used to assess changes in the morbidity of women taking tamoxifen chemoprophylaxis for breast cancer. The information was collected from reports by the women themselves during routine (6 monthly) visits to IBIS centres. Information was validated and then categorised using groups from the British national formulary (BNF). Data on 1279 women out of the 2531 recruited to the study in total (50.5%) reporting use of one or more drugs were included initially although the report is based on around on third of women (27%) of those recruited once inclusion criteria were applied.

Medications were excluded where there was thought to be no association with tamoxifen or where a precise reason for prescription would be difficult to obtain. Criteria were based on the literature review reported in Chapter 2 and independent medical advice was taken. Drugs excluded were, for example, antibiotics for self limiting illness such as chest infections, antimalarials and medications for chronic diseases such as diabetes or asthma as well as food supplements and analgesics for inappropriate causes such as bee stings.

The remaining medications were primarily concerned with cardiovascular symptoms (43.9%), for abnormalities of the endocrine system (12.2%) and for symptoms associated with the central nervous system (25.3%) - mostly for the treatment of depression. Drugs for migraine (6.9%) and the drug thyroxine (11.5%) were categorised separately.

Betablockers and calcium blockers account for the highest proportion of drugs prescribed for cardiovascular symptoms; these are used primarily for angina and hypertension. Lipid lowering drugs accounting for around 10% are primarily used for secondary prevention of heart disease though there is increasing use for primary prevention Of the 4 drugs used for the relief of breast pain evening primrose oil - the only non prescribed medication included - was the most frequent comprising 68% of

reports in the endocrine category. Thyroxine use was reported by 79 women. This drug is taken for underactive thyroid and for the relief of symptoms such as tiredness and lethargy. 174 women reported use of an antidepressant accounting for 85% of drugs for psychiatric symptoms. Migraine drugs were used by 80 women (though excluding Propanolol which can also be used for hypertension the number was 48 women).

Comparison of the rates of use of medications for women recruited to IBIS with that found in a large general practice (8,000 registered patients) provides face validity for the data set since the rates of use are comparable across all categories and for a number of specific drugs such as betablockers. For example, around 14.5% of women aged 45-64 were prescribed drugs for cardiovascular symptoms in general practice compared with 12% of women in IBIS and around 4 % of women are prescribed drugs for depression in the general practice compared with 7% of women in IBIS. The results are also comparable to those reported in the National Morbidity survey.

There are no significant differences between the 2 arms of the trial for any of the major categories of drugs or for any sub category although this may be due to the small numbers involved. Further recruitment is needed to fully elucidate any differences, which may exist. In particular there is a trend towards a difference in the use of betablockers between the 2 arms of the study; a sub group of drugs used for the relief of vascular symptoms such as hot flushes. The additional cost (or saving) in the use of betablockers is estimated at around £4 per woman per year.

This estimate is included in the sensitivity analysis for the model of cost effectiveness developed in Chapter 7. No morbidity estimate is included in the baseline case for the model because of the lack of sufficient evidence of either a difference in the use of prescribed medications or in the use of hospital visits (discussed in the previous Chapter) between women in the 2 arms of IBIS. Including an estimate for morbidity in the sensitivity analysis does however identify the range within which any impact on morbidity would bear on the cost effectiveness ratio. Prior to the development of the model for cost effectiveness, the following Chapter assesses any costs which might

accrue to the women themselves when taking chemoprophylaxis. An analysis of any impact on quality of life for women taking long term tamoxifen is also considered.

Chapter Six

Indirect Costs of Tamoxifen Chemoprophylaxis

Women in IBIS: Personal Costs and Quality of Life.

Introduction

This chapter sets out to assess the effect of tamoxifen chemoprophylaxis on the women themselves. Two main issues are considered. These are the impact on personal costs such as taking time off work and travel costs to health facilities for women taking tamoxifen chemoprophylaxis and the impact on quality of life. The former analysis identifies a range of estimates for personal costs, which are included in the sensitivity analysis for the cost effectiveness model in Chapter 7. A decrease or an increase in cost due to changes in quality of life is included neither in the baseline model or in the sensitivity analysis since there is no evidence in the analysis set out below to suggest that women taking long term tamoxifen experience any change in quality of life.

The cost effectiveness of breast cancer chemoprophylaxis will depend on its efficacy in preventing incidence and mortality from breast cancer. The acceptability of long term drug taking will however bear considerably on the success of the intervention in routine health care. Few studies have addressed the indirect costs or benefits associated with changes in quality of life or the compromises made by the women themselves in terms of personal costs of chemoprevention. This trade-off between benefit from life years gained and the costs of potentially lowered quality of life for the women themselves is explored further in this section. Costs are examined in terms of the personal costs of travel and time spent attending clinic visits. The results are discussed in terms of the potential reduced value of breast cancer chemoprophylaxis.

History of some previous illnesses particularly thrombosis or neoplasm renders women ineligible for taking long term tamoxifen. The physical health of women recruited to IBIS and indeed of all women likely to be eligible for tamoxifen prophylaxis is therefore likely to be equivalent to or better than women of the same

age and socio-economic status in the general population. It is possible however that there is some psychological morbidity associated with being at high risk for breast cancer though it is difficult to discern how this might be affected by tamoxifen prophylaxis. Fallowfield[175] has suggested that the effects may be bipolar with women's anxiety state being either ameliorated or exacerbated by inclusion in a trial depending on factors such as level of internal locus of control, personality and recent history of stressful life experiences such as bereavement.

Information on these issues was obtained by means of a questionnaire sent to a sample of women recruited to IBIS. The questionnaire had three parts, firstly using a standard health status instrument to assess quality of life, secondly a set of questions concerned with the personal cost of tamoxifen prophylaxis asking about the cost of travel, the cost of time off work and other costs associated with attending clinics and finally a set of questions concerned with how women perceive issues concerning breast care and breast examination in particular. The third group of questions was included by the IBIS co-ordinator to assess the impact of the study on the women's approach to personal breast care and are not discussed here.

Personal costs

Questions cover the cost and time of travel and any specific costs incurred because of attendance at the clinic such as childcare costs and time off work. The aim is to estimate the range and significance of personal cost in the overall cost of breast cancer chemoprophylaxis.

This set of questions was also used to assess the value women place on the possibility of taking tamoxifen for breast cancer prophylaxis in relation to the benefit they perceive from it. Two linked questions were asked: Firstly, about the level of efficacy - in terms of breast cancers prevented - at which they would be prepared to take tamoxifen. Secondly, the personal costs they might be prepared to incur (in terms of distance travelled) in order to receive the service. These questions are indicative of the women's perception of risk and benefit from tamoxifen prophylaxis. They provide a

basis for quantifying the cost women would be willing to bear in order to receive tamoxifen prophylaxis.

Quality of Life

The quality of life questionnaire is intended to inform the economic analysis about any possible decrement or increment in health status that may represent a cost for women taking tamoxifen chemoprophylaxis. Quality of life information is also of value in understanding issues such as compliance since changes in health status because of tamoxifen use may affect the willingness of otherwise asymptomatic women to comply with a long term daily drug regimen.

After careful consideration, information on quality of life was sought using the SF36 - a generic health related quality of life instrument[171]. This instrument met a number of requirements. Firstly it was considered important to use a measure which had demonstrated sensitivity to detecting small variation in the health status of normal healthy individuals. Women recruited into IBIS are drawn from the general population and are expected to be as healthy. Moreover the objective of treatment with tamoxifen in this context is to maintain health.

Secondly the SF36 has been shown to be better at detecting low levels of ill health than other quality of life instruments such as the Nottingham Health Profile[172]. Thirdly the reliability, validity, responsiveness and acceptability of the SF36 has been demonstrated in a number of settings with both healthy and disease specific populations[173]. Normative data for the SF36 are available by age and gender for the UK population which will allow comparison for women recruited into IBIS with the general population[174].

Finally, since a battery of other questions were to be included in the questionnaire it was essential that the quality of life instrument be short and acceptable. Many other quality of life measures were found to be too long or not to have been validated in large samples[175]. The SF36 was designed as a self-administered questionnaire[176]. It

contains 36 items and is intended to take about 5 minutes to complete. It measures health across 3 main health attributes on eight multi-item dimensions. The attributes are: functional status - including dimensions about physical functioning, social functioning and role limitations attributed to either physical or emotional problems, well being - covering mental health, energy (or fatigue) and pain, and finally an overall evaluation of health. This structure allows an assessment of the impact of tamoxifen chemoprophylaxis across all aspects of health. In 6 of the 8 dimensions respondents are asked to rate their responses on 3 or 6 point scales rather than as yes or no as in other questionnaires. For each dimension items are scored, coded and summed on a scale from worst health (0) to best health (100).

Method

The 3 sets of questions were piloted with a group of women in the study to assess acceptability and ease of response. While the women selected are a highly motivated group being representatives from each centre there was a 100% response rate from the 20 questionnaires sent out. Subsequent discussions at a meeting with the women suggested that they had experienced few problems completing the questionnaire and had welcomed the opportunity to address questions about general health and personal costs involved. Information was sought in particular on the understanding of the question about the level of effectiveness at which they would be willing to take tamoxifen and again understanding was high. None of the questions had been missed and most women had spent less than 20 minutes overall in completing the forms.

The final version of the questionnaire including the 3 sets of questions described above comprised: the quality of life instrument including 36 questions, a set of 13 questions concerned with feelings about breast cancer and breast care including the question about the level of effectiveness of tamoxifen prophylaxis at which women might be willing to participate in the programme and 5 questions concerning the personal cost of IBIS. A question was also added to elicit information about the socio-economic status of the women using occupational status from the General Household Survey. Information on age of the women and other characteristics could

be cross matched from their general IBIS record since the women were also asked to include their name and study number. The 3 sets of questions were put together into a booklet and sent to all women recruited to UK centres. A total of 2,380 questionnaires were mailed to all women recruited to the study using the address database correct at January 1st 1998 along with a newsletter and other information relating to IBIS. Most questionnaires were sent on July 10th 1998; a further 274 were forwarded to women three weeks later. A reminder was sent to all women alongside mailing of an information sheet at the beginning of September.

The covering letter sent with the questionnaire explained the context for the three sets of questions and stressed 2 main points. Firstly that the women should offer her immediate response to the questions not spending over long completing the questionnaire and secondly that there was no expectation at all that the health of women in IBIS was likely to be at all different from the general population.

A form was devised from the questionnaire so that the responses could be entered onto a database in oracle and the analysed using STATA. For analysis requiring knowledge of the randomisation status of the women the data was separated into 2 tables Q and L according to the 2 arms of the trial.

Results

The analysis is based on 1,557 questionnaires. This is an estimated response rate of 68.2% returned questionnaires. An error with the mailing machine resulted in the loss of around 10% of the questionnaires. The response rate is based on 2,380 questionnaires known to have been mailed and 1,624 returned. Of those returned 1,577 were completed and entered. 47 questionnaires were returned though not completed. The proportion of questionnaires returned and entered is 66.3%.

Costs of chemoprophylaxis to the women themselves

Costs to the women themselves arising from the cost of travelling to a clinic for chemoprevention; the costs of time off work and other costs involved such as childcare or maintenance are set out in the tables below.

1. Mode of transport

921 women (59%), travel to an IBIS centre using their own means of transport (see Table1). An additional 9% of women use their own transport in combination with public transport, a friend's vehicle and either walking or using a taxi. 23% of the women use public transport alone with an additional 7% using either their own vehicle, a friend's vehicle, a taxi or walking as well. At least 6% of women rely solely on a friend to transport them to the centre. Around 11% of women use two or more forms of transport.

Table 1. Mode of transport to IBIS Centres

Type of Transport	Frequency	%
Own	921	59%
Public	353	23%
Friend	92	6%
P&O	60	4%
O&F	26	2%
P&W	19	1%
Walk	17	1%
P&T	18	1%
P&F	15	1%
POW	8	1%
O&W	7	0%
Taxi	4	0%
F&T	2	0%
F&W	2	0%
POF	2	0%
PFT	2	0%
PFW	1	0%
OTW	1	0%
PTW	1	0%
missing	6	0%
Total	1557	100%

2. Time (m) spent travelling to the Centre

Table 2 shows that the median frequency for travel time is between 30-60 minutes. Almost 75% of the women spend longer than 30 minutes in travelling and half of those spend over an hour travelling to the centre.

Table 2. Travel time (m) to IBIS centres

Time	Frequency	%
<30 minutes	385	25%
30-60 minutes	573	37%
>60 minutes	592	38%
missing	7	0%
Total	1557	100%

3. Cost (£) of travel to the clinic

The cost women incur in travelling to IBIS centres are detailed in the Table 3. Over half of the women (58%) travel solely by car; a further 7% use the car supplemented by some other means of transport as well either public transport (3.5%), other (2.6%), public transport and taxi, (1%) or public transport and other, (1%). The mean cost of transport by car accounting for the use of petrol only was estimated at £5 per woman. Public transport only was used by 379 (24%) of the women and by a further 100 alongside the car (3.5%), taxi (1.6%), other (,1%), car and taxi, (1%), car and other (<1%), taxi and other, (1%) and car, taxi and other (<1%). The mean cost of public transport was estimated at £7.1. Taxis were used by 43(3%) of the women but only 9 used taxis alone. Almost 10% of women used 2 or more means of transport. Most of these used public transport and car or car and taxi or car and other; 16 women used 3 means of transport and 1 woman used 4 means of transport. 106 women did not complete this section. The mean costs overall from the estimates given by the women themselves were £6.1. The costs ranged from 60p to £200, the latter for travel by air for 1 woman in the study. The range of costs represents the low geographic spread of centres available for recruitment to IBIS and the willingness of some women to incur considerable travel cost in order to have the opportunity to participate in the trial.

Table 3. Costs of travel by mode of transport (£)

Mode of transport	number	Sum cost (£)	Mean cost (£)
Public(P)	379	2697.2	7.12
Car (C)	906	4543.4	5.0
Taxi (T)	9	73.5	8.2
Other(O)	14	40.5	2.9
P&C	55	804.1	14.6
P&T	26	378.5	14.6
P&O	3	54	18.0
C&O	41	503.8	12.3
T&O	1	175	175.0
P,C&T	5	75.9	15.2
P,C&O	10	153.8	15.4
P,T&O	1	11.0	11.0
P,C,T&O	1	0	0.0
missing	106	0	0.0
Total	1557	9510.6	
Mean cost			6.1

4. Time (m) spent at the clinic: first visit

It is clear that over half of the women in the sample (58%) spend over 41 minutes with almost a third spending longer than 60 minutes in the centre; around a third of women spend between 21 and 40 minutes in the centre. The median frequency is between 41 and 60 minutes. The 5% of women who spend less than 20 minutes on their first visit are most likely to have reported on their initial discussion pending recruitment to IBIS rather than their first full IBIS visit. The initial recruitment visit requires sufficient time for full discussion of the implications of the trial as well as the history taking, physical examination, blood test and mammography described earlier. Some IBIS centres explain a good deal about the trial process including issues concerning randomisation and the background to the study prior to the woman deciding to enrol in the study. 5% of women did not complete this section.

Table 4. Time (m) spent at first visit.

Time(minutes)	frequency	%
</=20	77	5%
21-40	496	32%
41-60	488	31%
>60	425	27%
missing	71	5%
Total	1557	100%

5. Time (m) spent in follow up visits.

The median time spent in follow up visits is between 21-40 minutes with 63% spending less than 40 minutes in the centre during follow up visits; a fifth spend less than 20 minutes. 14% of women did not complete this section.

Table 5. Time (m) for follow up visits

Time	Frequency	%
</=20minutes	326	21%
21-40	647	42%
41-60	252	16%
61+	115	7%
Missing	217	14%
Total	1557	100%

6. Other costs

The women were asked to specify other costs involved in attending an IBIS centre. The costs listed are for childcare or for loss of earnings including taking time from holiday entitlement in order to attend an IBIS centre. The other category includes expenditure on maintenance such as meals and snacks. 1,106 women recorded that no additional costs other than travel were incurred.

Table 6. Additional costs (£) incurred by women recruited to IBIS

Type of cost	(freq)	%	Sum cost (£)	Mean cost (£)
Child care(C)	3	0%	35.3	11.8
Lost pay(LP)	94	6%	2620.6	27.9
Holiday(H)	91	6%	2944.9	32.4
Other(O)	128	8%	773.2	6.0
None(N)	1106	71%	0	0
C&LP	4	0%	128.5	32.1
C&H	3	0%	177.0	59.0
C&O	3	0%	37.0	12.3
LP&H	3	0%	267.0	89.0
LP&O	8	1%	467.3	58.4
H&O	4	0%	119.8	30.0
C&LP&O	1	0%	15.0	15.0
LP&H&O	1	0%	114.0	114.0
Missing	108	7%	7699.5	
Total	1557			
Mean cost(£)	4.94			

Only 343(22%) women reported incurring additional costs other than travel when attending IBIS centres. The largest group - 128 women (8%) record 'other' costs which relate mostly to food and drink purchased while travelling to or attending IBIS centres. The mean cost was estimated by these women as £6.0 per women. For the 106(7%) of women who recorded loss of earnings through attending the clinic the mean cost is £27.9 for lost pay alone; 12 women record additional costs either through taking holiday entitlement as well (3), other costs (8) or holiday entitlement and other costs(1). For the 91 women (6%) who take holiday entitlement in order to attend clinics the mean cost estimated by them is £27.9. A very small number of woman (1%) incur childcare costs which reflects the age range of women recruited to IBIS; most are unlikely to have pre-school age children.

7. Main Occupation

Table 7 shows that a large proportion of the women (62%) are employed either full or part-time; a further 8% are self-employed. 14% of the women describe themselves as retired and 13% record that they work mainly in the home. Very few (2%) describe their main occupation as undertaking charity work and only 2% are unemployed.

Table 7. Main Occupation

Occupation	Frequency	%
Employed full time	545	35%
Employed part time	414	27%
Retired	223	14%
Work mainly in the home	199	13%
Self employed	117	8%
Do charity work	28	2%
Unemployed	25	2%
Missing	6	0%
Total	1557	100%

8. How women value tamoxifen prophylaxis

Responses to the questions concerning the value women place on tamoxifen prophylaxis (Tables 8&9) suggest that the women recruited to IBIS are highly motivated and willing to travel some considerable distance to receive the service.

All of the women who returned questionnaires completed the section designed to assess the value women place on taking tamoxifen prophylaxis in relation to the numbers of deaths likely to be prevented per year. Table 8 shows that 60% would be willing to take tamoxifen prophylaxis at a relatively low level of absolute risk reduction with 1 death prevented per year. A further 17% of women expressed a willingness to take tamoxifen at the highest stated level of risk reduction (preventing 5 deaths per year) with the remaining responses ranged in the middle of the distribution.

Table 8. Willingness to take tamoxifen prophylaxis in relation to numbers of deaths prevented per year.

Deaths prevented	Frequency	%
>1	933	60%
>2	123	8%
>3	163	10%
>4	44	3%
>5	264	17%
Missing	30	2%
Total	1557	100%

Table 9 shows how far women would be prepared to travel to receive tamoxifen prophylaxis at the level of risk reduction expressed above.

Table 9. Willingness to travel to receive Tamoxifen prophylaxis

Travel to:	Frequency	%
Local GP	14	1%
Local hospital	219	14%
Specialist centre	1311	84%
Missing	13	1%
Total	1557	100%

The responses show a very clear willingness to travel to specialist centres at least 5 miles away.

9. Total time and travel costs involved in attending IBIS centres.

Table 10 is set out as a summary of the per woman personal costs associated with recruitment to IBIS. The costs are based on the estimates of travel time and time spent at the clinic both for the first and subsequent visits described earlier. The travel time and time spent at the clinic has been costed at average hourly earnings for all women. Including the wage cost of time spent is in line with the employment status of the

women in the study; very few (2%) report themselves as unemployed compared with 62% who report being in full or part time paid employment. The national earnings survey was used to cost time for women in the age groups recruited to IBIS and childcare costs were taken as an average of estimates available from the study of Employers and Childcare published by Incomes Data Services. The costs of journeys to and from the IBIS centres are taken from the cost estimates given by the women themselves with the addition of 4% non fuel variable costs for travel. Using a reimbursement cost per mile travelled was considered. This would be extremely difficult to apply since the kinds of cars used by the women were not known. Weighting the cost in terms of the loss of time involved valued at average earnings provides an estimate of the willingness of these women to participate in a trial with the opportunity to take tamoxifen prophylaxis. This can be compared with the sensitivity analysis also included in the table which values travel times at zero. The costs of loss of pay are also taken from the estimates given by the women themselves. A sensitivity analysis included in the table values the loss of pay at average earnings and loss of holiday entitlement at half-average earnings.

Table 10. Estimates of personal costs for women recruited to IBIS using time costed at zero or alternatively at average hourly earnings.

			Average	Costing
			earnings	Time@0
	per visit	per 5 years	Cost(£8.7/hr)*	
Median time spent in travel to the centre (50m)	100	1000	145	0
Median time spent per woman per 1st visit	50	50	7.25	0
Time spent per woman per follow up visit	30	270	39.15	0
Total time		**1320**	**191.4**	0
Mean cost of travel(£)per woman +4% non fuel variable cost	£12.69	126.9	18.3976	18.3976
Other expenditure per woman ^	£4.94	49.4	7.163	7.163
Total cost (£)per 5 years			**216.9606**	**25.5606**
Total cost per woman per year			**43.39212**	**5.11212**

*Cost of travel estimated by the women in IBIS plus 4% non fuel variable costs

*Average hourly earnings for women aged 40-59 in full time work. Taken from the New Earnings Survey. Part A. ONS published by HMSO. April 1998

**Average childcare costs. Taken from Employers and Childcare. Study no 633 published by Incomes Data Services in September 1997

^ Including loss of pay as loss of average earnings and loss of holiday entitlement as loss of half pay assuming 4 hours taken in total changes this estimate to £5.5

The amount of time spent travelling to or attending clinics over 5 years of taking tamoxifen prophylaxis is estimated as 4.4 hours per year. Including the costs of this time using the average earnings for women in this age group along with the reported costs of travel and other costs involved in attending IBIS clinics gives an estimated cost per woman per year of £43.4. The cost assumptions are changed in the sensitivity analysis. Firstly assuming that the costs of time are not included (i.e. costed at zero) reduces the costs per woman per year to £5. Secondly, the costs of loss of earnings or loss of holiday entitlement is included at average annual earnings rather than at the level of lost pay reported by the women. This changes the overall analysis very little since there is little difference in the costs reported by the women and those taken from Incomes Data Services. The cost per woman per year is estimated at around £43 or £215 over 5 years.

10. Visits to GP

601(39%) report having visited their GP in the last 4 weeks; 956(61%) had not. Of those who had, the outcome of the visit is listed in Table 12. For 63% of the women the visit resulted in a prescription. For 284(46%) this was for a prescription alone, 39 (6%) report receiving a referral and a prescription and a further 29 (5%) received a referral to the practice nurse or other member of the primary health care team and a prescription. A small proportion of women (3%) reported a referral to hospital and to the practice nurse as well as receiving a prescription. For 76(12%) the visit had resulted in a referral to hospital and 89(14%) had a consultation only with the doctor

resulting in neither referral nor prescription. 41(7%) of the women had a referral to the practice nurse or other member of the primary care team with an additional 4(1%) being referred to hospital and to the practice nurse or other member of the primary health care team. 12 women (2%) did not complete this section though they did state they had seen their GP in the last 4 weeks. 16 women stated that they had not visited their GP in the last 4 weeks but completed the section on the outcome of the visit: 13 reported receiving a prescription only, 1 also visited the practice nurse, 1 received a referral to hospital 1 had a consultation with the GP only.

Table 12 Outcome of visits to GP

Outcome from GP visit	frequency	%
Consultation only (C)	89	14%
Referral to hospital (R)	76	12%
Prescription only (P)	284	46%
Appointment with nurse (V)	41	7%
GP and practice nurse	10	2%
Referral and prescription	39	6%
Referral and practice nurse	4	1%
Prescription and practice nurse	29	5%
CRP	4	1%
CPV	12	2%
RPV	16	3%
CRPV	2	0%
Missing data	12	2%
Total	618	100%

Of the women who visited their GP in the last 4 weeks a computation was made of which study arm they had been randomised to. This was only possible for the 352 women (65%) who also declared their study number on the survey sheet. The results were that 169/352 (48%) were on treatment A and 183/352 (52%) were on treatment B. There is no significant difference between the two treatment arms.

Quality of Life

Table 13 below shows the results for scores on each of the dimensions of the SF36 including the missing data in each case. In general proportion of missing data was

low. Instructions for the SF36 were followed for dealing with the missing items. This was as follows:

- Physical Functioning is scored from a 10 item question with missing data calculated from the answered items; for 11 scores no average could be calculated.
- Social Functioning is scored from 2,two item questions. Where scores were missing the missed score is assumed to be equal to the answered item; there were 5 missing scores where neither item had been answered.
- Role Limitation (physical) is scored from 1, four item question; missing responses were calculated as the average of answered items
- Role Limitation (emotional) is calculated from 1, three item question; missing responses are calculated as an average of answered items
- Pain is taken from 2, two item questions; missing scores are assumed to be equal to answered items. There were 12 questions where both items were omitted
- Mental health was scored from 5 items of a single question; missing data were calculated as the average of completed items; there were 11 uncompleted responses where calculating an average was not possible
- Energy is calculated from 4 items of a single question, averages are taken to calculate missing scores; there were 10 responses were an average could not be calculated
- General Health Perception was calculated from 4 items of a question and a second question as a 5 item score. Averages across completed items were taken for missing items where possible; there were 4 completely missing scores
- Change in health status compared with a year ago is scored from a single question; there were 14 missing responses

Table 13. Summary scores for the SF36 for IBIS women compared with results from a study of the general population.

Attribute	Physical functioning	Social functioning	Role Limitation	Role Limitation	Pain	Mental Health	Energy Fatigue	General Health
IBIS women			(physical)	(emotional)				Perception
N	1546	1552	1557	1557	1545	1546	1547	1553
missing data	11	5	0	0	12	11	10	4
Mean	*83*	*84*	*80*	*80*	*76*	*74*	*59*	*73*

Standard deviation	21.8	22.9	34.7	34.7	24.6	17.1	21	20.1
Rank	2	1	3	3	5	6	8	7
GP Sample(women aged 45-54)[174]	***85***	***87***	***82***	***81***	***77***	***73***	***59***	***73***
N	**917**	**973**	**960**	**965**	**950**	**957**	**965**	**950**
Rank	**2**	**1**	**3**	**4**	**5**	**6**	**8**	**6**

In general the distribution of scores shows that the women perceive themselves to be healthy across the range of dimensions particularly for physical functioning, social functioning, role functioning (physical) and role functioning (emotional). The perception of general health is also high. The scores for mental health are more widely distributed with a mean of 74. For pain, a significant proportion of women perceives themselves as having some bodily pain reducing the mean score to 76. Women recruited into IBIS perceive energy and fatigue as the lowest scoring health dimension; the mean score is 59.

A comparison with results from a population survey reporting 'norms' for health status is included in the table (in bold). The results included are for women aged 45-64 from a postal survey based on a random sample taken from the computerised family health service register in 4 health districts[174]. The comparison suggests that the health of women recruited to IBIS does not differ from that of women of the same age in the general population. The ranking of scores for the IBIS group and for the general population sample is similar. Physical and social functioning rank highest in both the general population sample and the IBIS group with mental health pain scores and scores for general health lower. Energy and fatigue is the lowest ranked score in both groups.

A final question asked within the SF36 is concerned with change in health status over the last 12 months. Scores are much lower in this section because a score of 100% would mean much better health and of 0% would be much worse health. The mean score was 51.9 % (SD=14.8) which suggests that women recruited to IBIS report the same or improved health compared with the previous year.

Differences in the 2 arms of the trial

Table 14 below shows the means and standard deviations from the SF36 for each of the health dimensions separated for women in the 2 arms of the trial notionally referred to as Q and L. The results from t tests for each health dimension are also included.

Table 14. SF36 summary scores and t-test for women allocated to either Q or L representing the 2 arms of the trial.

			Q	L
Physical functioning		mean(n)	83.7(511)	85.1(471)
		std dev	21.1	20.1
		t	-1.082	
		p>t	0.279	
Social functioning		mean(n)	83.8(513)	85.5(474)
		std dev	23	22.3
		t	-1.157	
		p>t	0.2472	
Role Limitation		mean(n)	81.9(513)	82.7(478)
(physical)		std dev	33.7	32.9
		t	-0.409	
		p>t	0.682	
Role Limitation		mean(n)	81.3(513)	81.4(478)
(social)		std dev	33.9	33.6
		t	-0.763	
		p>t	0.9392	
Pain		mean(n)	75.9(512)	77.9(475)
		std dev	23.9	24.4
		t	-1.302	
		p>t	0.193	
Mental health		mean(n)	74.1(511)	75.5(473)
		std dev	17.2	17
		t	-1.285	
		p>t	0.198	
Energy		mean(n)	58.9(513)	60.7(473)
		std dev	21.3	21.4
		t	-1.278	
		p>t	0.201	
General Health		mean(n)	72.4(513)	73.7(475)
		std dev	20.2	20.4
		t	-0.951	
		p>t	0.342	
Change from		mean(n)	52.0(512)	51.6(468)
1 year ago		std dev	14.5	14
		t	0.432	
		p>t	0.6658	

None of the results suggest that women in the 2 arms of the trial are different in respect of any aspect of health status. There are clearly no adverse effects on general quality of life for women taking tamoxifen prophylaxis. Neither do women in one arm or the other consider their health to have deteriorated over the last year.

Discussion

The personal costs for women in IBIS range from £20 to £30 per year of recruitment depending on whether time spent travelling to or during clinic visits is included at zero base or costed at average hourly earnings for women in this age group. The impact of these costs on the overall cost effectiveness of tamoxifen chemoprophylaxis is discussed in Chapter 7.

Responses from the questionnaire show that a high proportion of women recruited to IBIS are car owners who spend between £5-7 on their journeys to IBIS centres. Most of the women have either full or part time employment although only 14% of the women claim to lose money through attending an IBIS clinic. *There may be some underestimation of these costs since women may disregard there own personal expenditure when undertaking health care. In particular, women recruited to IBIS are self selected and the motivation to seek recruitment to a trial may lead them to place relatively low value on the cost of time spent, travel or other incidental expenditure.*

Less than 1% of the women say they have responsibilities for children that would cause them to incur additional cost while they are attending the centre. The wide range of travel costs reported includes over 75% of journeys lasting 30-60m or more than 60 minutes; 10% of women use 2 or 3 different forms of transport. This finding of a willingness to travel to distant sites in order to participate in a trial with the chance of receiving tamoxifen is supported by the responses showing a high value placed on receiving tamoxifen even at the lowest stated level of absolute risk reduction despite the need to travel to specialist centres.

The extent to which travel costs including the time spent travelling would be incurred outside the trial setting will depend on the terms of any possible extension given to the license for use of tamoxifen following completion of the UK trial. If licensing is extended to include prophylactic use then access through GP practices might be possible which would reduce travel time and personal costs for women seeking this service. Under such a model of care it is possible that time spent in follow up would reduce though an initial referral to a specialist breast unit may continue to be needed to secure eligibility for long term treatment with tamoxifen. Time spent during visits to IBIS is higher on the first than on subsequent visits with a mean of 40-60 minutes for the first appointment compared with 20-40 minutes for follow up.

The impact of quality of life effects from tamoxifen prophylaxis has been recognised by study investigators for both the UK and USA trials though to date there are no published reports available from these studies. The economic consequences of changes in health status are likely to be threefold. Anxiety among women at high risk for breast cancer may have consequences for counselling needs which should be addressed within the health service. This would be particularly important if there was a profound increase in anxiety among women taking tamoxifen prophylaxis. Changed anxiety or other effects of tamoxifen prophylaxis on quality of life may also affect compliance with the drug regimen and with appointment keeping.

The similar ranking and level of scores for most of the health dimensions for the SF36 Quality of Life instrument in the IBIS population in comparison with a general population sample does however suggest that there is little or no effect on quality of life for women recruited to IBIS. Low scores for pain recorded in both IBIS women and the general population sample have also been observed in other general health surveys for women of this age. The high ranking of mental health scores for women in IBIS compared with the general population is interesting. While this result is not significant it does suggest that recruitment to the trial does not have an adverse effect. Fallowfield has suggested that for women at high risk for breast cancer the possibility of participation in a prevention trial may improve their quality of life by raising their locus of control and reducing anxiety.

The results for t-tests between the 2 arms of the trial shows that no adverse effects of quality of life occur for women taking tamoxifen, neither has health changed over the last year for women taking tamoxifen or for those in the control arm. These results may be biased by a possible tendency of women likely to have a high quality of life and health status being most willing to put themselves forward for trial entry. It is noticeable that the score for physical health for women in the study remains high suggesting no adverse effects of symptoms or side effects from taking tamoxifen affect these women. Mental health remains close to the scores for the general population shown in Table 13 for women in both arms of the study suggesting no adverse effects on mental health for women in either group. Indeed women's health in both groups is no different than for women of a similar age in the general population. Costs in terms of any possible decrement on quality of life for women taking tamoxifen are minimal These results suggest that no adjustment would be needed to calculate quality adjusted life years gained for women willing to undertake this kind of treatment.

Other issues concerning biases in this study should be considered. The response rate to the questionnaire was less than 70%. This may have been a low estimate since the precise number of questionnaires mailed was unknown due to an error with the mailing machine. It does however raise questions about the possible characteristics of women failing to complete or not receiving the form. An undertaking was given to the women both in the covering letter forwarded with the questionnaire and the reminder letter that completion was entirely voluntary. In the interests of meeting this commitment and not compromising possible continuance of any women with the study it was not possible to seek further information from the women failing to respond.

Biases associated with volunteers are also relevant in this context and may result in a more positive health report among those responding. Volunteer bias documented for example in screening programmes suggests that people who choose to participate are likely to differ from the general population in a number of ways that may affect

reported health. In general volunteers tend to have better health and lower mortality rates than the general population and are more likely to adhere to prescribed regimen. On the other hand those who volunteer for IBIS may have an increased risk of mortality or morbidity than the general population. Such individuals may be more likely to score lower for aspects of quality of life than the general population. The direction and magnitude of this bias is difficult to predict though will be considered in further follow up.

In more general terms, it could be argued that asymmetry may also exist in the sample because of a differential drop out rate between the 2 arms of the trial. Those women most likely to suffer adverse consequences on quality of life as a result of taking tamoxifen may be more likely to drop out of the study than those experiencing no effects or indeed net benefits. As a consequence, decrements in general health and well being will have been underrepresented in the sample taken. In addition the results presented here do not, of course, include longer term effects. Further research is needed to assess the extent to which women involved in the trial are representative of all those who may be eligible for tamoxifen prophylaxis.

Summary and Conclusions

Costs to the women themselves are measured in order to assess any possible reduction in the value of breast cancer chemoprophylaxis caused by unreasonable personal costs for the women involved. This includes both the cost of work lost due to clinic visits, costs of travel to the clinics or other costs associated with clinic visits and possible decrements in quality of life for women taking tamoxifen prophylaxis.

Due to the eligibility criteria for IBIS the women recruited might be expected to be as healthy if not healthier than women of the same age in the general population with the possible exception of possible psychological morbidity due to being at high risk for breast cancer. Compliance with a long term drug regimen will rely on the trade off women are prepared to make balancing a possible future benefit against possible side effects or reduced quality of life.

Personal costs and quality of life were assessed by means of a questionnaire piloted and then sent to all women in the study (as at January 1st 1998). Two main sets of questions were included. The first set dealt with travel cost, the cost of time lost, work lost and other specific costs such as the cost of childcare. The second set concerned with quality of life and health status used the SF 36, a specific instrument validated in populations with low levels of ill health. Normative data have been published for the SF36 and it is a short and acceptable form to complete. The response rate was 68% though not all forms were completed; the analysis is based on 66% of the forms.

A large proportion of women recruited to IBIS report themselves to be in part time or full time work (62%) although few women report loss of earnings due to an IBIS visit (7%). Personal car use is the most frequent form of transport to the centre involving over 70% of journeys and 75% of journeys are longer than 30 minutes with half of these being over 1 hour.

The women are characterised by their willingness to travel. A question concerning the value they place of tamoxifen prophylaxis suggests that over 60 % would wish to take it at a low level of absolute benefit (1 death prevented per year) and that 84% of women would be happy to travel to a specialist centre to receive tamoxifen. The costs used for travel are those reported by the women themselves with a 4% non-fuel variable cost. The National Earnings Survey was used to cost time off work. Sensitivity analysis included time lost, costed at average earnings and at zero cost. The costs of travel range from 60p to £200; the mean costs of travel are £6.1. The total mean cost summarised across all costs including the cost of travel, time spent and other costs is an estimated £217/ 5 woman years when time is included at average earnings and £25.56/ 5 woman years when time is costed at zero.

A question was included about recent visits to the GP in order to assess any differences between the 2 arms of the trial in use of primary care. 39% of the women overall reported a visit to the GP in the last 4 weeks; 63% of these visits had resulted

in a prescription. There was no difference in the pattern of use of primary care between the 2 arms of the trial.

Responses to the SF36 show that women recruited to IBIS have the same pattern of health as women in the general population across all of the health dimensions including physical functioning, role limitation (includes both physical and emotional), social functioning, pain, mental health energy/fatigue and general health perception. Energy and fatigue has the lowest score for both groups. There is also no significant difference in any of the health dimensions between the 2 arms of the trial. There appear to be no adverse effects on quality of life for women taking long term tamoxifen prophylaxis and no adjustment for quality of life is needed in assessing cost effectiveness.

The impact of personal costs to the women themselves on cost effectiveness of tamoxifen chemoprophylaxis are discussed further in Chapter 7. The estimates derived from the analysis discussed above are included in the sensitivity analysis for cost effectiveness. The range of estimates used identifies the level at which personal costs begin to bear adversely on the cost effectiveness ratio.

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Chapter Seven

Economics of Tamoxifen Chemoprophylaxis for Reducing Mortality and Morbidity from Breast Cancer.

The following section sets out a population based cost effectiveness analysis for prophylaxis of breast cancer with the drug tamoxifen. The data were collected from women enrolled in the International Breast Cancer Intervention Study (IBIS); costs directly related to research in the trial are not included. The design is based on a decision model assessing the health and economic outcomes of chemoprophylaxis for women at different levels of risk for breast cancer compared with no chemoprophylaxis.

Assumptions used in both the baseline model and in the sensitivity analysis are based on the data presented in previous chapters. This includes summary data from the analysis of service delivery for tamoxifen chemoprophylaxis reported in chapter 3, the possible range of costs associated with changes in morbidity reported in chapter 4 for the rate of use of hospital visits by women in the 2 arms of the trial and in chapter 5 for the use of medications. A range of assumptions for costs associated with travel to the centres and the loss of earnings for the women themselves are included based on the analysis presented in chapter 6. Costs associated with changes in quality of life are not included since the analysis also shown in chapter 6 found no evidence of differences in health status and quality of life between women in the 2 arms of IBIS. Cost associated with the risk of adverse events includes only the increased risk of endometrial cancer since information based on the literature review in Chapter 2 minimises the likelihood of other major mortality risks. The estimate for the cost of breast cancer included in the model is taken from the analysis developed below.

The determinants for cost effectiveness are derived from modelling the impact of tamoxifen chemoprophylaxis on a district health authority population. The outcome - cost per breast cancer prevented - is assessed against alternative assumptions for cost and for efficacy of chemoprophylaxis. More detailed analysis for the cost per life year gained for women taking tamoxifen chemoprophylaxis is modelled on a cohort of women at high risk (an incidence of breast cancer of 6.76/1000) with estimates for

risk reduction taken from the NSABP P-1 study[2]. This model includes estimates for cost effectiveness with different assumptions about the duration of the protective effect of tamoxifen in reducing the risk of breast cancer. This approach is further developed to produce an estimate of the likely extreme difference in cost per life year gained depending on the lowest or highest assumptions associated with the costs of service delivery, costs associated with morbidity and with the women's personal costs.

Core Assumptions

In the baseline case, a decision model is prepared to compare the health and economic outcomes of breast cancer chemoprophylaxis for women in an average district health authority with a population of one million. The average population risk of breast cancer is used to set the predicted numbers of cases. It is estimated that 7% of the women in each of four, five year age bands (45 - 64) have at least a two fold increased risk of breast cancer (this risk is distributed as 5% at two fold relative risk, 1% at five fold relative risk and 1% at 10 fold relative risk) and would be eligible for tamoxifen chemoprophylaxis. The baseline incidence in the population for each age band in the model is taken from the Public Health Common Data Set for England and Wales. Efficacy is estimated at 50% reduction in incidence of breast cancer for women taking tamoxifen chemoprophylaxis based on the finding from the North American NSABP P-1[2], though the impact of a lower estimate of efficacy on the cost effectiveness ratio is determined in the sensitivity analysis. The efficacy of prophylaxis is assumed to be equivalent for women across all levels of risk. Core assumptions about the model of service delivery is of specialist hospital based care with significant involvement of specialist nurses. Other models of care considered in the sensitivity analysis are a service based in primary care; the impact on cost effectiveness of assumptions about the costs of service delivery included in IBIS is also assessed.

Outcome estimates for the analysis set out below are made from the predicted endpoints for women involved in IBIS and for changes in breast cancer incidence from those reported in the NSABP P-1 chemoprevention trial referred to earlier. The potential impact of tamoxifen chemoprophylaxis on morbidity is discussed even though there were no significant findings from the blinded subgroup analysis of

reported morbidity in the 2 arms of IBIS presented earlier (Chapters 4 and 5). Specifically there are 2 scenarios that seem feasible based on current evidence. These are the costs associated with the use of betablockers and the costs associated with changes in the rate of hospital visits for benign breast disease.

Breast cancer treatment costs are derived from an audit of diagnosis and management of 1,779 breast cancer cases from 17 different hospital Trusts carried out by the Thames Cancer Registry (TCR) [17]. This is described in detail below. The 17 Trusts included in the TCR breast cancer audit database all provide complete and comparable data. The patients represent 48% of the total of North Thames Region's activity of 3039 new cases of breast cancer diagnosed between January 1st 1996 and December 31st 1996[17].

In the model, the marginal cost of chemoprophylaxis compared with no chemoprophylaxis is expressed as the cost per breast cancer prevented and per year of life gained. Projections are also included about the potential for years of life gained based on survival estimates. The marginal cost effectiveness is the additional cost of prophylaxis minus any cost savings due to the use of prophylaxis (savings from breast cancers prevented and any other beneficial health effects) divided by the number of cases of breast cancer (under 65) averted. Cost per life year gained is based on average expectations of survival for women in each age band. Economic outcomes are the cost of prophylaxis and the changed cost of treating breast cancer. Estimates with discounting of both costs and benefits are included.

Costs of breast cancer

The cost of breast cancer averted is taken from the Thames Cancer Registry Audit of New Cases of Breast Cancer. The audit was used because it is more likely to provide estimates of the true cost of breast cancer treatment than a protocol based cost study. A number of studies have shown that there are wide variations in the quality of care in relation to published standards. The audit was however carried out at a time when there was widespread discussion in the medical press about the importance of implementing an agreed protocol for management of breast cancer and nationally agreed guidelines had been published. It is likely therefore that the variations in

estimate of £200 per woman available to clinics participating in IBIS. Developments in the model also look at the potential impact of costs or savings which may arise from changes in the morbidity experience for women taking long term tamoxifen particularly the cost of treatment for symptoms of benign breast disease or for changes in the cost of beta blockers prescribed for the vascular symptoms such as hot flushes which are commonly associated with tamoxifen. Variations are also proposed in the numbers of women eligible for prophylaxis including targeting only women at very high risk of breast cancer and the possibility that all women over 55 might be eligible. Finally, the impact of the costs to the women themselves is included by using two different assumptions about the value of the time spent by women in travelling to and attending clinics. These are time valued at average hourly earnings for women of the same age or with time valued at zero. Other personal costs such as childcare are reviewed.

Results

Cost of breast cancer

The frequency of each of the procedures for women diagnosed with breast cancer noted during the TCR audit and the costs based on charges is set out in Table 1. The procedures appearing with the highest frequency in the audit are for clinical assessment (91%), mammography (74%) and cytology (80%). This is in line with NHS guidance from the Clinical Outcomes Group[40] which states that a definitive diagnosis on the majority of women presenting with a breast lump (95%) should be made on the basis of triple assessment by clinical assessment, breast imaging and cytology by fine needle aspiration or core biopsy. In general the use of frozen section histology should only be needed in a small proportion of cases. Trucut biopsy was used in 23% of cases in the TCR sample. This is likely to have been used in addition to cytology by fine needle aspiration in some cases.

The use of mammography seems rather low. In general, patients receive full blood count, urea and electrolytes, liver function tests and chest X ray as a baseline to surgery. Blood counts, urea and electrolytes are not listed in the TCR sample though are assumed to be included in the charges associated with surgery. The use of liver function tests and chest X-ray does seem to be low in the sample given that 80% of

women receive surgery. This may be due to variations in the local protocol for care among the different hospitals included or in underreporting. The cost of these interventions is small in relation to the overall cost and variations in practice are unlikely to affect the overall cost of care. Other tests such as bone scan and liver ultrasound are not routinely indicated since they do not have a high yield in asymptomatic patients with operable breast cancer and there is no evidence that there use improves survival or quality of life[184].

The radiotherapy regimen proposed by the Royal College of Radiologists suggests a rather higher frequency of use than the 50% recorded in the TCR audit. The difference may well be explained by variations in mastectomy rates around the North Thames Region and the local policy in relation to radiotherapy. Although radiotherapy has been shown to reduce local recurrence in patients undergoing local excision of a breast lump, there is still no conclusive evidence on the value of radiotherapy in improving local control following mastectomy. Current conclusions from overviews of randomised trials suggest that there is no survival benefit from radiotherapy and that deaths from other causes may increase with radiotherapy following mastectomy[180, 186]. An ongoing trial (START) presently still recruiting patients will provide more detailed information to resolve this issue. Until the completion of the START trial, rates of radiotherapy are likely to vary according to local policy. At just under £1500 per patient the overall cost of radiotherapy is 24% of the total charges for breast cancer care - a surprising proportion considering the paucity of research evidence to guide practice. It is interesting to note also that the cost of treating advanced disease with high cost chemotherapy amounts to a small proportion of the total cost (<0.6%) while these treatments remain accessible to only a small proportion of the population.

Table 1. Charges for breast cancer care

	Costs of new cases of breast cancer				
	Procedure	**Price**	**%**	**Cost(£)**	**Note**
	clinical assessment	147	91	133.77	1
	mammogram	28	74	20.72	1
	ultrasound	30	30	9	1
	cytology	8	80	6.4	1
	trucut biopsy	20	23	4.6	1
	chest X ray	12	38	4.56	1
	bone scan	138	19	26.22	1
	liver ultrasound	30	20	6	1
	liver function tests	5	28	1.4	1
	women undergoing surgery		80	0	
	excision biopsy	562	19	106.78	2
	wide local excision	661	45	297.45	3
	repeat excision	562	4	22.48	2
	mastectomy	1472	28	412.16	4
	cavity wall biopsy	562	3	16.86	2
	reconstruction	1,472	3	44.16	5
	women prescribed tamoxifen	120	77	92.4	6
	ovarian ablation	1914	2	38.28	7
	chemotherapy	754	21	158.34	8
	lymphoedema	147	2	2.94	9
	Radiotherapy	48	10	4.8	10
	following lumpectomy	3000	80(45%)	1080	
	following mastectomy	2250	60(45%)	378	
	Advanced Disease			0	
	5 year follow up	3540	80	2832	11
	% advanced disease		12	0	
	%non anthracyclines	160	3	4.8	
	%anthracyclines	1648	7..5	123.544	

	%taxoids	8000	0.4	32	
	% palliative care	285	85	242.25	12
	Total			6101.914	

Notes

1 Hospital outpatient cost of test

2 HRG (j07)[159]

3 HRG (j04)

4 HRG(j02)

5 HRG (j02)

6 Non proprietary cost of prescribing tamoxifen(20mg tabs)[16]
@ £2.95 for 30 tabs)/yr

7 HRG (m03)

8 Cost of triple combination of cyclophosphamide[16]
methotrexate and 5-flouracil(CMF)8 cycles.

9 General surgery outpatient cost for management of lymphoedema[15]

10 Radiotherapy costs taken from Mount Vernon Cancer Centre

11 Mytomycin C:dose of 12mg/m2,doxorubicin:dose of 65mg/m2,paclitaxel: dose of [16]
Costs of 10 outpatient oncology visits also included

12 Cost of palliative care/patient

Costs for endometrial cancer

The estimated increase in the incidence of endometrial cancer for women taking long term tamoxifen is taken from the relative risk for women taking tamoxifen found in the NSABP P-1 chemoprevention trial. An overall annual average rate of 2.3 per 1000 women in the tamoxifen arm compared with 0.91 in the placebo group this is a relative risk of 2.53 (95% CI = 1.53 - 4.97). This information is used in the model to estimate the expected increase in the incidence of endometrial cancer for the baseline case and for varying assumptions about the efficacy of treatment. The baseline rates for endometrial cancer are estimated at 3 per 10,000 for women in England and

Wales. Background rates in the USA are considerably higher. The cost of endometrial cancer is estimated as £2,261 per woman.

Results

Baseline case (core assumptions)

The cost effectiveness of tamoxifen chemoprophylaxis is based on information presented in Tables 2 and 3. Table 2, presents the baseline model for the estimated numbers and cost of breast cancer in an average English District Health Authority with a million population including a total of 120,140 women in the eligible age group for tamoxifen prophylaxis (45 – 64). The expected incidence of breast cancer for these women is shown by age group. Seven percent of the women in this population (8,410) are estimated as having at least a two fold relative risk of breast cancer because of family history and to be eligible to receive prophylaxis. The table approximates the number of cases per year likely both for women at average population risk (188) and for those at increased risk (28). The cost of breast cancer care for the total number of new cases (216.49) is just over a million pounds (£1,320,994) per year.

Table 2. The expected number (and cost) of cases of breast cancer for a health district (population of 1,000,0000 with 120,000 women aged 45-64)

			Women at least 2 fold risk					cost of
		Incidence	increased risk	2Xrr		baseline risk	total	breast cancer (£)
Age	Number	Rate/100,000	number (7%)	Incidence	cases/year	cases/year	cases/year	6102
45-49	35,100	125	2457	250	6.14	40.80	46.95	286,466
50-54	34,240	134	2396.8	268	6.42	42.67	49.09	299,567
55-59	26,060	185.5	1824.2	371	6.77	44.96	51.73	315,627
60-64	24,740	259.6	1731.8	519.2	8.99	59.73	68.72	419,334
Total	120,140		8,409.8	1,408.2	28.33	188.16	216.49	**1,320,994**

In the baseline case for tamoxifen chemoprophylaxis, shown in the first column of Table 3, it is assumed that efficacy is a 50% reduction in breast cancer incidence per year for the 5 years duration of tamoxifen use for women with at least a two fold risk of breast cancer. It is assumed that all women at high risk (8,410) comply with a regimen of daily tamoxifen for five years. The estimated cost effectiveness is £57,558 per breast cancer prevented.

Sensitivity Analysis

1. Changes in assumptions about efficacy and eligibility

Table 3 compares the results for the cost per breast cancer prevented in the baseline case with results for changes in assumptions about efficacy of tamoxifen chemoprophylaxis and for a scenario where all women over age 55 are eligible for chemoprevention with 50% uptake.

Table 3. Cost per breast cancer prevented in the baseline case (Risk Reduction (RR) =0.50) and with a series of alternative assumptions about Risk Reduction.

	Risk Reduction (RR)							
	Baseline case							
	RR=0.50	n	RR=0.45	n	RR=0.33	n	RR=0.5	n
Cost of chemoprevention							50%55+	
Cost of delivery	£4,499,243	8409.8	£4,499,243	8,409.8	£4,499,243	8409.8	£1,713,7013	32031.8
Cost of adverse events	£8,727.7	3.9	£8727.7	3.9	£8,727.7	3.9	£54964.9	24.3
Total(cost)	£4,507,970.7		£4,507,970.7		£4,507,970.7		£17191977.9	
Savings from chemoprevention								
Breast cancers prevented/year	£86,420.2	14.2	£77,778.2	12.7	£57,728.7	9.5	£247314.1	40.5
Breast cancers prevented (5 years)	£432,101.1	70.8	£388,891.0	63.7	£288,643.5	47.3	£1236570.3	202.7
Total(savings)	£432101.1		£388891.0		£288643.5		£1236570.3	
Cost per breast cancer prevented	**£57,558.2**		**£64,631.5**		**£89,197.7**		**£78,733.8**	

The cost of delivering a service for tamoxifen chemoprophylaxis using the estimate of £535 per woman in a specialist hospital based service (from Chapter 3) for 8,410 eligible women is £4,499.243. This cost remains the same when varying the assumption about efficacy since the same numbers of women are treated in each case. For the scenario where women can opt into the programme once over age 55, the cost of delivering chemoprevention increases by around 3 fold in order to treat around 32,000 women in addition to those at high risk for reasons other than age. The cost of treating the 21 additional cases of endometrial cancer which might be expected to arise with such a large number of additional women taking prophylactic tamoxifen outweighs the savings in cost terms from the 26 additional breast cancers prevented.

Estimates for the cost effectiveness (cost per breast cancer prevented) of tamoxifen prophylaxis shown in Table 3 increases by over 50% when efficacy is estimated at only 0.33 reduction in risk of breast cancer. The cost effectiveness does not improve when increasing the numbers of women taking tamoxifen with eligibility determined by age since the cost of service delivery rises at a greater rate than the numbers of breast cancers prevented. In the same way, the impact of adverse events on overall costs remains the same. Despite a relatively low unit cost for service provision in comparison with many other health care interventions the overall costs are high. This is because a large number of women must be treated in order to prevent one breast cancer. The absolute risk reduction in this Health Authority population model is 0.007. The numbers of women who would need to receive tamoxifen in order to prevent one breast cancer is 142.

2. Alternative means of service delivery: Model based on the budget available to participating centres in the International Breast cancer Intervention Study (IBIS)

Table 4 sets out the estimates for tamoxifen prophylaxis based on the expenditure assumptions used in IBIS. The expenditure is set at £200 per woman recruited. The cost per breast cancer prevented is £17,773.4 for the baseline case with an assumed relative risk reduction of 0.5. This estimate rises to £29,639.6 for the lowest assumption of relative risk reduction at 0.33 and is £20,426.2 at 0.45.

Table 4. Cost effectiveness (Cost per breast cancer prevented) of chemoprevention based on the expenditure assumptions in IBIS with a series of assumptions of relative risk reduction.

	Risk Reduction (RR)							
	RR=0.50	n	RR=0.45	n	RR=0.33	n	RR=0.5	n
Cost of chemoprevention							50%55+	
Cost of delivery	£1,681,960.0	8,410	£1,681,960	8,410	£1,681,960.0 0	8,410	£6,406,360.00	32,031.8
Cost of adverse events	£8,727.7	3.9	£8727.7	3.86	£8727.7	3.86	£54,964.9	24.3
Total(cost)	£1,690,687.7		£1,690,688		£1,690,687.7		£6,461,324.9	
Savings from chemoprevention								
Breast cancers prevented/year	£86,420.2	14.2	£77778.2	12.75	£57728.7	9.46	£247,314.1	40.5
Breast cancers prevented (5 years)	£432,101.1	70.8	£388891.0	63.7	£288643.5	47.30 31	£1236570.3	202.7
Total(savings)	£432,101.1		£388891.0		£288643.5		£1236570.3	
Cost per breast cancer prevented	**£17,773.4**		**£20,426.2**		**£29,639.6**		**£25,782.2**	

Table 5 shows the equivalent data for the service delivery option of offering tamoxifen prophylaxis in primary care. The most cost effective option of £42,713.1 per breast cancer prevented is seen with a risk reduction of 50% for a service based in primary care. This model would include consultation with specialists only at the first and final visits.

Table 5. Cost effectiveness of chemoprevention based on the expenditure assumptions in a GP led model in a primary care setting with a series of assumptions of relative risk reduction.

	Risk Reduction (RR)							
	RR=0.50	n	RR=0.45	n	RR=0.33	n	RR=0.5	n
Cost of chemoprevention							50%55+	
Cost of delivery	£3,448,018	8409.8	£3,448,018	8409.8	£3,448,018	8409.8	£1,313,3038	£32,031.8
Cost of adverse events	£8727.7	3.9	£8727.7	3.9	£8727.7	3.9	£54964.9	24.3
Total(cost)	**£3,456,745.7**		**£3,456,745.7**		**£3,456,745.7**		**£13,188,002.9**	

Savings from chemoprevention								
Breast cancers prevented/year	£86,420.2	14.2	£77,778.2	12.7	£57,728.7	9.5	£24,7314.1	40.5
Breast cancers prevented (5 years)	£432101.1	70.8	£388891.0	63.7	£288643.5	47.3	£1236570.3	202.7
Total(savings)	£432,101.1		£388,891.0		£288,643.5		£1,236,570.3	
Cost per breast cancer prevented	£42,713.1		£48,137.0		£66,974.5		£58,975.7	

Impact of risk

Table 6 uses a simple model to illustrate the impact of risk in the population on cost effectiveness of prophylaxis (Cost per breast cancer prevented). Using the same parameters as for the model above in the tables above, changes in cost effectiveness are calculated for a population of 1,000 women at three different levels of risk of breast cancer (two fold, five fold and ten fold of baseline risk) with the three different estimates for efficacy described above (risk reduction of 0.33,0.45 and 0.5).

Table 6. Impact on cost effectiveness (cost per breast cancer prevented) of the relative risk of breast cancer in the targeted population

Cost per breast cancer prevented (£)			
	Relative risk		
Risk reduction	**2fold**	**5fold**	**10fold**
0.33	89,197.7	36,899.5	17,839.5
0.45	64,631.54	27,073.0	12,926.3
0.5	57,558.2	24,243.7	11,511.6

The cost effectiveness estimate ranges from £89,197.7 to £11,511.6 for women at two fold increased risk with a reduction in the incidence of breast cancer of 0.33 to women at ten fold increased risk with a reduction in risk of 0.5 respectively. The costs are primarily determined by the numbers of women receiving tamoxifen. The cost effectiveness is lowest for groups of women at very high risk for breast cancer as increasing numbers of breast cancers are prevented.

3. Impact of changes in morbidity

The possible impact of changes in morbidity for women taking tamoxifen included here are based on results from women enrolled in IBIS discussed earlier. Although, in general, there were few apparent differences in hospital visits or in use of prescribed medications - the proxy measures used for morbidity - for women in either of the two arms of the trial, the results did suggest a need for continued review with increasing accrual to the trial. In particular from the hospital visit data there was a non significant trend indicating the possibility of changes in symptoms of benign breast disease requiring specialist advice and/or hospital treatment and from the medications data, changes in the use of beta blockers.

The relative risk reduction for benign breast disease for women taking tamoxifen was calculated for women enrolled in IBIS using the hospital visits data which suggested that there was a non significant difference of about 5% in the numbers of women having hospital visits resulting in a procedure, between the 2 arms of the trial. Moreover the visits in one arm of the trial tend to be lower cost than in the other arm (a mean of £650.35 compared with £827.16). The baseline rate of hospital visits by women in the relevant age group was taken as around 17% from the NHS hospital episode system per year[167]. For the baseline District Health Authority model where 8,410 women are receiving tamoxifen this might result in a difference in the cost of hospital visits of £32-£41 per woman per year receiving tamoxifen. Since the trial has not yet concluded it is necessary to assess these effects as a difference between the two arms of the trial. This is a cost - or a saving - on the overall cost of delivering tamoxifen chemoprophylaxis per woman of between 30 and 38%.

For possible changes in the use of betablockers the impact is smaller. The rate of use of betablockers in the general population was estimated as 5.6% of a general practice population aged 45-64 (87/1,565). The relative risk between the 2 arms of the trial was 0.67. Assuming that the frequently used drug, Atenolol, is prescribed at 50 mg/day at a cost of £1/month the cost or saving from tamoxifen prophylaxis would be an estimated £7 per woman. This is less than 0.2% of the total cost of tamoxifen chemoprophylaxis..

The impact of changes in morbidity are considered for cost effectiveness (Cost per breast cancer prevented) in Table 8.

4. Impact of personal costs to the women themselves

The analysis in Chapter 6 found a range of personal costs per woman per year from £5 to £43 depending on whether or not the time spent by women in travelling to and attending clinics is included at average earnings or at zero. Table 7 shows the effect on the cost per breast cancer prevented for the baseline case in the District Health Authority model with an assumption of 0.50 reduction in incidence of breast cancer based on a population where women at 2 fold increased risk of breast cancer are eligible to take tamoxifen. Table 7 shows both personal cost estimates.

Table 7. Cost effectiveness (Cost per breast cancer prevented) of tamoxifen chemoprophylaxis including two assumptions about the women's personal costs

			Risk reduction=0.50	n
Cost of chemoprevention			£	
	Cost of delivery		4,499,243.00	8,410
	Cost of adverse events		8,727.68	3.8600982
	Women's personal costs	@ £5	42,049.00	
		@ £43	361,621.40	
	Total(cost)	**@ £5**	4,550,019.68	
		@ £43	4,869,592.08	
Savings from chemoprevention				
Breast cancers prevented/year			86,420.22	14.16
Breast cancers prevented (5 years)			432,101.10	70.8
	Total(savings)		432,101.10	
Cost per breast cancer prevented		**@£5**	58,151.99	
Cost per breast cancer prevented		**@ £43**	62,664.89	

The cost per breast cancer prevented increases by between 1% and 8% compared with the baseline estimate of £57,558.2 shown in Table 3.

5. Consolidated estimate for cost per breast cancer prevented

Table 8 sets out a summary cost effectiveness for tamoxifen chemoprophylaxis for breast cancer based on the analysis in Table 12. In this summary it is assumed that the protective effect of tamoxifen endures only during the period of active intervention. Estimates for cost effectiveness would of course improve were there to be a longer term protective effect. Alternative estimates for the impact of findings for morbidity and for personal costs to the women themselves are included. For the latter, both estimates of £5 and £43 per woman per year in the nurse led and IBIS model are included. In the GP model of service delivery the personal costs are included either as £5 or at zero cost. This latter assumption is based on the expectation that most care will take place in the GP practice with minimal cost to the woman herself. Under this model, a single visit to the specialist centre may occur once during the 5 year period and the £5 personal cost assumption represents a high estimate for the cost women may have to bear for a hospital visit.

The table shows that the highest estimate for cost per breast cancer prevented is £40,645 in a nurse led service when the highest estimate of personal cost for the women and themselves is included and when assuming that costs accrue because of tamoxifen use due to increased incidence of benign breast disease and increased use of beta blockers. In the scenario with costs for beta blockers accruing to chemoprophylaxis but with a reduction in the rate of benign breast disease the cost per breast cancer prevented is £14,423.5. The lowest cost per breast cancer prevented is obtained where the cost of service delivery approximates to the budget available to participating IBIS centres of £200 per woman and where personal costs to the women are set at £5 per woman.

In the GP led service which, based on available information may be a feasible approach a negative value for cost effectiveness of - £3990.83 is obtained where tamoxifen use is considered to reduce the rate of benign breast disease and increase the use of beta blockers. This suggests that benefits exceed costs and arises partly because it is assumed in the GP led service that there will be no or few personal costs to the women themselves. The cost effectiveness is £12,426.19 when both aspects of

morbidity accrue as costs. These results demonstrate the impact of both personal costs and the possible impact of morbidity on overall cost effectiveness.

Table 8. Summary estimates for cost effectiveness of tamoxifen prophylaxis for breast cancer for hospital based, GP led or IBIS cost for service delivery including or excluding estimates of impact of morbidity (benign breast disease or use of beta blockers) and personal costs for women at £5 or £43 per woman for the nurse led and IBIS service models and £5 or £0 personal cost for woman in the GP model of service.

Service delivery & personal cost assumptions	**Morbidity Assumptions**			
	plus benign breast disease **plus** beta blockers	**minus** benign breast disease **minus** beta blockers	**plus** benign breast disease **minus** beta blockers	**minus** benign breast disease **plus** beta blockers
Cost effectiveness for nurse led service(£535/woman) assuming £43 personal cost per woman.	40,644.60	24,083.64	40,534.93	24,193.31
Cost effectiveness for nurse led service(£535/woman) assuming £5 personal cost per woman.	30,874.78	14,313.82	30,765.10	14,423.49
Cost effectiveness for GP led service(£410/woman) assuming £0 personal cost per woman.	12,426.19	(4,100.51)	12,350.78	(3,990.83)
Cost effectiveness for GP led service (£410/woman) assuming £5 personal cost per woman.	24,468.13	7,919.95	24,371.24	8,029.63
Cost effectiveness for IBIS model (£200/woman) assuming £43 personal cost per woman.	23,474.78	6,948.09	23,399.38	7,057.76
Cost effectiveness assuming IBIS costs(£200) and £5 personal cost per woman	12,681.94	(3,844.75)	12,606.54	(3,735.08)

6. Cost per life years gained

Table 9 shows the years of life gained for women taking tamoxifen prophylaxis. The model in this case is based on the annual incidence of breast cancer found in the NSABP P-1 Breast Cancer Prevention Trial. The results were monitored over six years. Mortality from all causes of 324.6 per 100,000 is taken from age specific mortality for women aged 35-64 in England and Wales included in the Public Health Common Data set for 1998 based on data for 1995-7. Women in the placebo arm of the trial had an average incidence of breast cancer of 6.76 per 1000 for women.

The model assumes that there is no further protection from tamoxifen beyond the 6 year monitoring period and the incidence of breast cancer reverts to that of the control population. In Table 8 different assumptions for the length of the protective effect are included. Under three different possible outcomes of an additional 5, 10 or 15 years continuous protective effect it is assumed that women in the tamoxifen arm retain a relative risk of reduction in incidence of breast cancer of 0.5.

Table 9. Net reduction in incidence of breast cancer. The core assumption in this table is of no further protective effect beyond year 6. The average rate of breast cancer is 6.76/1000. Deaths from all causes are assumed to be an average mortality rate of 324 per 100,000 woman years.

Year	Breast cancer incidence				Deaths from all causes		Breast cancer free population surviving		Net reduction in incidence
	control	tam	RR	multiplier	control	tam	control	tam	
	0.0067				0.00324		100,000	100,000	0
1	670	448.9	0.33	0.67	324	324	99,006.0	99,227.1	221
2	663.3	298.5	0.55	0.45	320.8	320.8	98,021.9	98,607.8	365
3	656.7	400.6	0.39	0.61	317.6	317.6	97,047.5	97,889.6	256
4	650.2	331.6	0.49	0.51	314.4	314.4	96,082.9	97,243.6	319
5	643.8	199.6	0.69	0.31	311.3	311.3	95,127.8	96,732.7	444
6	637.4	286.8	0.55	0.45	308.2	308.2	94,182.3	96,137.7	351

7	631.0				305.2		93,246.1		631
8	624.7				302.1		92,319.2		625
9	618.5				299.1		91,401.6		619
10	612.4				296.1		90,493.0		612
11	606.3				293.2		89,593.5		606
12	600.3				290.3		88,703.0		600
13	594.3				287.4		87,821.3		594
14	588.4				284.5		86,948.3		588
15	582.6				281.7		86,084.1		583
16	576.8				278.9		85,228.4		577
17	571.0				276.1		84,381.2		571
18	565.4				273.4		83,542.5		565
19	559.7				270.7		82,712.0		560
20	554.2				268.0		81,889.9		554
21	548.7				265.3		81,075.9		549
Total	12755.7							Total	10,790
								Net reduction in incidence	1966.0

The result for the assumption of no further protection beyond year 6 is a net reduction of breast cancer incidence of 1966 at year 21, 15.4% of the total number of cases of breast cancer (12,755.7) overall in this high risk population during the time period. Using the same approach the results for three alternative assumptions in the duration of the effect, an additional 5, 10 or 15 years of protection, yields a reduction of 3,513, 4,984 and 6,383 cases of breast cancer respectively. These estimates are used in Table 10 to assess the impact of the duration of the protective effect on the marginal cost effectiveness.

Table 10. Cost per breast cancer prevented and per additional breast cancer free life year gained with a series of assumptions about the duration of the protective effect of chemoprevention for 100,000 women at high risk (6.76 per 1000) for breast cancer. The table is based on hospital based service delivery (£535/woman).

		Protective effect (duration in years) beyond year 6			
Cost		0	5	*10*	*15*
Cost of delivery at £535 per woman	£53,500,000.0				
Cost of adverse events	£103,779.9				

Total cost	£53,603,779.9				
Savings from breast cancer	£11,990,430	£11,990,430	£21,436,326	£30,412,368	£38,949,066
Net reduction in breast cancer incidence		1966	3513	4984	6383
Cost per breast cancer prevented		**£21,166.5**	**£9,156.7**	**£4,653.2**	**£2,295.9**
Life years gained		*9,825.0*	*35,130.0*	*74,760.0*	*127,660.0*
Cost per life year gained		**£4,235.5**	**£915.7**	**£310.2**	**£114.8**

For each possible outcome of an additional 5, 10 or 15 years in the duration of the protective effect, Table 10 shows the cost effectiveness of tamoxifen chemoprophylaxis. For an additional 5 years gained the estimate for cost per breast cancer prevented decreases by over 60% to £9,156.7. Gaining an additional 10 or 15 years of protection results in a cost per breast cancer prevented of £4,653.2 and £2,295.9 respectively.

The calculation of cost per life year gained also shown in Table 10, assumes that women with no protective effect beyond year 6 have gained 5 years of life during the first protective phase. Women who gain an additional 5,10 or 15 years have a net gain of 10, 15 and 20 years respectively. The cost per life year gained is £4,235.5 for the base case with no additional years gained beyond year 6. Cost effectiveness estimates range from £915.7 to £114.8 per life year gained for gains of 10 to 20 years duration of the protective effect.

Discounted cost effectiveness is shown in Table 11. Costs and benefits are discounted to net present value at 5% per year using the public sector discount rate. Costs are discounted at 5 % over 5 years and the benefits are discounted at 5% over 5, 10, 15 and 20 years according to the additional years of the protective effect (0,5,10,15 years respectively). Thus a breast cancer prevented was valued more highly in year 1 than in later years and the costs of tamoxifen prophylaxis are considered more expensive in the early than later years. Results in Table 9 are shown for the hospital based model of service delivery at £535 per woman. Results for a GP led model at £410 per woman are summarised in Italics.

Table 11. Discounted cost per breast cancer prevented and per additional life year gained with a series of assumptions about the duration of the protective effect of chemoprevention for 100,000 women at high risk (6.76 per 1000) for breast cancer. Costs are discounted at 5% over 5 years and savings are discounted at 5% over 5,10,15and 20 years respectively according to the years of protective effect (0,5,10, and 15years respectively). The table is based on hospital based service delivery at £535/woman. Results for a primary care led service at £410 per woman are included in italics.

		Additional Protective Effect (years)			
Costs		0	5	10	15
Cost of delivery at £535	£53,500,000.0	£41,917,250.0	£41,917,250.0	£41,917,250.0	£41,917,250.0
Cost of adverse events	£103,779.9	£81,311.6	£81,311.6	£81,311.6	£81,311.6
Total cost	£53,603,779.9	£41,998,561.6	£41,998,561.6	£41,998,561.6	£41,998,561.6
Savings from breast cancer		£9,394,501.9	£13,159,760.5	£14,628,349.0	£14,679,903.0
Net reduction in breast cancer (discounted)		1540.4	2156.6	2397.3	2405.8
Cost per breast cancer prevented		£21,166.5 ***(14,808.4)***	£13,372.2 ***(8,831.0)***	£11,417.1 ***(7,331.8)***	£11,355.6 ***(7,284.4)***
Life years gained		7697.9	21566.3	35959.6	48115.1
Cost per life years gained (specialist based service delivery)		£4,235.5	£1,337.2	£761.1	£567.8
Cost per life years gained (primary care led service delivery)		***£2,963.2***	***£883.1***	***£488.8***	***£364.2***

The (discounted) marginal cost per breast cancer prevented is £13,372.2 for 5 years additional benefit beyond year 6 and a marginal cost per breast cancer prevented of £11,355.6 per breast cancer prevented for a protective effect continuing for 15 years. The discounted marginal cost per life year gained is £567.80 with a protective duration of 15 years.

7. A high and low cost scenario for cost effectiveness

Table 12 shows a number of estimates for cost effectiveness of tamoxifen chemoprophylaxis using contrasting assumptions to determine the extent of the extreme difference between a high and low cost scenario. For the high cost scenario the model of service delivery is assumed to be a specialist hospital based model. Morbidity is considered to accrue to the cost of service delivery both for benign breast disease and for use of beta blockers. The personal costs to the women associated with the hospital based model are £43/woman. The results are expressed as the cost per breast cancer prevented and per life year gained for the assumption of either a 5 or 10 year duration of protective effect. The low cost scenario is based on a GP model of service delivery and assumes that there are morbidity benefits for women taking tamoxifen prophylaxis resulting in both reduced use of beta blockers and hospital visits for benign breast disease. The low estimate for personal costs to the women themselves of £5/woman is included. For both scenarios the costs are discounted over 5 years and the savings over 5 or 10 years respectively.

Table 12: Cost effectiveness of tamoxifen chemoprophylaxis. A high and low cost scenario (based on the net incidence estimates set out in Table 9).

(a) Scenario 1: Highest Cost

Duration of Protective effect				
			5 (baseline case)	**10**
Costs (discounted)				
Service delivery (at £535/woman)			£41,917,250.0	£41,917,250.0
Adverse events			£81,311.6	£81,311.6
Beta Blockers (£7/woman)			£548,450.0	£548,450.0
Benign Breast Disease (£41/woman)			£3,212,350.0	£3,212,351.0
Personal costs (£43/woman)			£3,369,050.0	£3,369,050.0
Total cost			£45,759,361.6	£45,759,361
Savings				
Breast cancer prevented			£9,394,501.9	£5,795,089.5

No.s of breast cancers prevented			1966	3513
Discounted breast cancers prevented			1540.4	2156.6
Cost per breast cancer prevented			£18,496.9	£11,376.1
Discounted years of life gained			7697.9	21,566.3
Cost per year of life gained			£4,724.0	£1,853.1

(b) Scenario 2: Lowest Cost

Duration of protective effect				
			5 (baseline case)	10
Costs				
Service Delivery (410/woman)			£32,123,500.0	£32,123,500.0
Adverse events			£81,311.6	£81,311.6
Personal costs (£5/woman)			£391,750.0	£391,750.0
Total cost			£32,596,561.6	£32,596,561.6
Savings				
Beta Blockers (£7/woman)			£548,450.0	£429,730.0
Benign breast disease (£41/woman)			£3,212,350.0	£2,516,990.0
Breast cancer prevented			£9,399,282.8	£13,159,760.5
Total savings			£12,611,632.8	£15,676,750.5
Nos. of breast cancers prevented			1966	3513
Discounted breast cancers prevented			7697.9	21566.3
Cost per breast cancer prevented			£10,165	£4,816
Discounted years of life gained			9825	25130
Cost per year of life gained			£2,034.1	£481.6

The results for the cost per breast cancer prevented range between £18,496.9 and £10,165.3 per breast cancer prevented for the high and low cost scenario respectively

assuming a 5 year duration of protective effect. This is an extreme difference of £8,331.6. Where the duration of protection is for 10 years the cost per breast cancer prevented is £11,376.1 and £4,816.3 for the high and low cost scenario respectively. This is an extreme difference of £6,559.8. For cost per life year gained, the extreme difference between the high and low cost model for a 5-year duration of protective effect is £2,127.8 from £4,724.0 and £2,596.2 per life year gained respectively. For a 10-year duration of protective effect the difference is £1,068.6 from £1,853.1 per year of life gained to £784,5 per year of life gained respectively. These results suggest that there is only a small impact of morbidity and indeed of women's personal costs on the cost per life year gained. The main cost drivers are the cost of service delivery and the risk status of the women involved. The differences found between the 5 and the 10-year duration of protective effect are reduced by the process of discounting the benefits of chemoprophylaxis. Since this is a preventive intervention it could be argued that the benefits should not be discounted. Without discounting the benefits (years of life gained) the extreme differences between the low and high cost scenarios are lower particularly for duration of effect for 10 years. The extreme differences are £1667.2 per life year gained for a 5-year duration of protective effect and £656 for a 10 year duration.

Discussion

Chemoprophylaxis for breast cancer is targeted at a group of women at extremely high lifetime risk of breast cancer for whom few effective treatment strategies are available. Two different approaches are taken in developing estimates of cost effectiveness. Both yield similar results and provide complementary information about the factors affecting cost and cost effectiveness. Firstly, the decision analysis based on an average District Health Authority population of a million people provides an assessment of the importance of the risk status of the population. Where the absolute benefits of chemoprevention are low, high costs will accrue from the need to treat large numbers of women in order to prevent or delay a single breast cancer. Moreover in an average District Health Authority population the proportion of women at high risk will be relatively small. Secondly in the assessment from a cohort of women using results from NSABP P-1[2] it is clear that the cost effectiveness of tamoxifen chemoprophylaxis is favourable in comparison with many other health care

interventions when targeted at high risk women and providing that the protective effect continues beyond the period of active treatment.

Estimates of cost effectiveness based on the results from the NSABP P-1 study are more likely to represent the true magnitude for cost effectiveness since the population targeted is at high risk for breast cancer and the incidence in both the treated and control population was monitored assiduously over a number of years. The risk factors defining eligibility for the study and indeed those underpinning IBIS are a useful basis for defining a target population for tamoxifen prophylaxis in health policy. The cost effectiveness range is within the range of many routine treatments in the NHS and low for those concerned with preventing early mortality.

There are however a number of limitations to this analysis including a number of assumption used in the estimates for cost effectiveness. The results for cost effectiveness can only be expressed in terms of breast cancer incidence since to date there is no information about the possible effects on mortality. There is also no evidence to address the question of whether the results for incidence represent a delay in the development of cancers or a permanent benefit. There has been some speculation of an increase in the proportion of aggressive breast cancers owing to the selection of tamoxifen resistant tumours. The effectiveness of adjuvant tamoxifen for women taking tamoxifen at the time of diagnosis is not known and the mortality rate for these women may be high. Long term adverse effects of prolonged tamoxifen use will be monitored by ongoing follow-up in the UK and USA studies though only the known increase in risk of endometrial cancer has been included.

Fixed costs for any of the interventions discussed are not included since they are integrated within the charges used to derive cost estimates. Given the small numbers of women who might be eligible for chemoprophylaxis within the average health district it is likely that any increased demand would be absorbed within present breast cancer services or indeed in general practice. Moreover fixed costs would vary considerably in different centres and the emphasis here is on determining the main factors affecting cost effectiveness. Where implementation of a service for tamoxifen chemoprophylaxis was considered the fixed costs would bear on the start up costs. In deriving the estimates for cost effectiveness compliance is assumed to be 100% which

has not been the case in any of the chemoprevention studies to date. Reduced compliance may not affect the cost of service delivery, though will reduce the efficacy of the intervention. The precise impact of reduced compliance has not been calculated though is arguably likely to be comparable to the effect found for changes in efficacy seen in Table 6.

It is likely that a reduction in compliance would have its main effect on cost effectiveness through reducing the numbers of breast cancers prevented. Based on the figures shown in Table 10 a reduction in compliance to 70% would reduce the cost per breast cancer prevented to £32,854 (assuming that the savings from 30% fewer breast cancers prevented would be £8,396,352 instead of £11,990,430). This would change the cost per breast cancer prevented to £32,854 instead of £21,166.5 shown in the table - a difference of just over 50%. The impact on the difference in cost per year of life saved would be a change from £4,235.5 to £6,570.85. The effect of reduced compliance may be less were the cost of service delivery and the cost of adverse events also to be reduced. The effect of the former is however likely to be small especially if women continued to attend clinic sessions for checks but were not complying with appropriate ingestion of tamoxifen on a daily basis. The impact on adverse events may also be small since the costs associated with adverse events are relatively low in comparison with the cost of breast cancers prevented.

The cost of delivering tamoxifen prophylaxis per women is relatively low in comparison with many other health care interventions yet the overall cost effectiveness estimates are substantially influenced by the numbers of women who would need to be treated in order to prevent one breast cancer because of the level of absolute risk reduction. For women at moderate or low absolute risk of breast cancer this number is relatively high in comparison with the numbers of breast cancers prevented.

Cost effectiveness decreases with increasing risk of the women involved and measured over the six year period of the NSABP P-1 where the average risk in the population treated was 6.76 per 1000 becomes an estimated discounted cost per breast cancer prevented of £21,166.5 in a hospital based service (see Table 10). This

assumes that there are no additional benefits beyond the period of the active intervention and that all visits by the women are to specialist centres.

At a discounted cost per breast cancer prevented of £14,808.4 offering prophylaxis through general practice would be more cost effective than a hospital based service albeit nurse led with specialist support. Such an approach might be possible with only 1 visit to a specialist at the initiation of tamoxifen prophylaxis and anticipating a reduced number of follow up visits. It could be argued that mammography would be needed only to check eligibility for tamoxifen and that routine mammograms for a service which is intended to reduce the risk of breast cancer is an inappropriate intervention and an unnecessary expense outwith the routine NHS Breast Screening Programme. The IBIS estimate for cost effectiveness approximates the lowest estimate found for a GP based model of service delivery. It is likely however that the research costs for IBIS underestimate the true cost of the intervention with some subsidy from the host breast care services in the NHS.

Using the results from Table 12 the cost effectiveness of tamoxifen chemoprophylaxis appears to lie between £4,724 and £784.5 per life year gained. The former assumes a specialist hospital based model of service delivery with costs of morbidity for benign breast disease and beta blockers both accruing to overall costs and with the personal costs to the women themselves at the high estimate of £43 per woman. The estimate is based on the assumption that the duration of the protective effect for tamoxifen prophylaxis is 5 years beyond the active period of treatment. By contrast, the low estimate includes only £5 per woman for personal costs. Morbidity is assumed to be a net benefit to a woman taking tamoxifen for both benign breast disease and for use of beta blockers. The duration of the protective effect is 10 years. Although there is a three fold difference between the high and low estimates the cost per life gained appears to lie within a feasible range for a new health technology though would of course depend on the importance of defining and successfully targeting a high risk population.

There is some debate about the appropriateness of discounting in the context of prevention[19]. The effect is to reduce the value of future benefits undermining the relative value of prevention over therapeutic interventions. The consequence of

discounting is to increase the cost per life year gained particularly once costs have become more distant and benefits extend to an additional 15 years of protective effect.

Morbidity arising from tamoxifen prophylaxis appears to be low with little overall impact on cost effectiveness. To date, no comparable estimates have been published in other chemoprevention trials. Recent reports about the impact of the main adverse events of tamoxifen chemoprophylaxis particularly an increased risk of endometrial cancer suggest that the extent of the risk and the clinical impact have been exaggerated.

Developing the model for chemoprevention within the context of a district health authority population has the advantage of identifying the impact on the costs of breast cancer care overall. For an average District Health Authority population the impact on breast cancer incidence would be small. This is mostly because the proportion of the population with levels of risk of breast cancer high enough to become eligible for chemoprophylaxis are small. Where a programme for prophylaxis was developed eligibility criteria would be need to be strictly enforced in order to ensure that only high risk women were targeted. Failure to achieve a high risk population may result in expenditure on chemoprevention at the expense of more cost effective means of reducing mortality and morbidity from breast cancer.

Of importance in targeting tamoxifen chemoprophylaxis are findings from the NSABP P-1[2] trial that a benefit from tamoxifen was identified for women across the spectrum of risk factors and levels of risk. The trial was not designed to assess whether findings for high risk women could be generalised to all women and the main effect - of almost 50% reduction in risk of breast cancer occurs for a population of women at high risk. The study did however provide evidence that women with a history of LCIS or atypical hyperplasia were more likely to develop invasive cancer than had been previously expected and that tamoxifen chemoprophylaxis could reduce the risk. The authors conclude that eligibility should be extended to three main groups of women: women with a history of atypical hyperplasia or LCIS, the group of women under 50 with sufficient risk to warrant eligibility to the NSABP P-1 trial and postmenopausal women at high risk for breast cancer who have had a hysterectomy.

Since women in these categories are likely to have an average relative risk of at least 3 fold relative risk they may be appropriate criteria for targeting women in the UK.

The cost effectiveness estimates can be compared with other means of reducing breast cancer incidence although there are problems of comparability particularly in estimating the savings from the cost of breast cancer prevented. Boer and de Koning[187] published cost effectiveness estimates for the current NHS Breast Screening Programme of £25,142 per death prevented and £24,205 or £27,865 for extending the age range to 65 or reducing the interval to two years respectively. The estimates for tamoxifen prophylaxis are likely to fall well below this range providing that the intervention is targeted at women at high risk for breast cancer (at least 3 fold relative risk) delivered in general practice and that the effect of risk reduction translates into a mortality benefit.

The cost effectiveness of early treatment for breast cancer to year 10 of between £10,625 ($17,000) per death prevented for women at all ages in the highest risk categories to £31,250 ($50,000) for women at any age at a lower risk of death is lower than that found for breast screening. The effectiveness of early treatment for breast cancer may be considered comparable to the findings from NSABP P-1 since interventions are concerned with women at increased risk of death from breast cancer rather than with women at average population risk.

There is insufficient information on the present management of women at high risk for breast cancer to compare with the costs estimated for chemoprophylaxis of breast cancer. Bilateral prophylactic mastectomy has been a treatment choice for some women though there are few routine data available to assess the frequency of use of this approach, its survival advantage or cost effectiveness[88]. Annual mammography has also been suggested for women in high risk categories though there are no data at present to assess the efficacy of this approach.

Summary and Conclusions

Modelling cost effectiveness for tamoxifen chemoprophylaxis based on both a district health authority population and on the results from NSABP P-1 highlights the

importance of the cost of service delivery in calculating overall cost effectiveness. Estimates of the costs of service delivery and the possible costs of morbidity included in the model are taken from analysis of women recruited to the International Breast Cancer Intervention Study and presented in previous chapters. The baseline case is taken as a consultant based service in a hospital setting with specialist nurse involvement costing overall £535 per woman. This model of service delivery requires women to travel to specialist centres for treatment but restricts consultant input to an initial visit to determine eligibility and to exclude the possibility of breast cancer. Measures of efficacy are taken from outcome data published from the NSABP P-1. The costs of breast cancer have been developed from analysis of an audit carried out by the Thames Cancer Registry (TCR). Other costs such as for endometrial cancer are based on HRGs currently in use for costing procedures in the NHS.

Few studies have been published on which to base cost estimates for the treatment of early breast cancer. The TCR audit used here is based on 1,779 cases of breast cancer in 17 different hospital trusts in the Thames region. The cost of breast cancer is estimated at £6,102 per woman and includes estimated costs for advanced disease and for palliative care taken from the published literature. A large proportion of the overall cost is for radiotherapy (24%); the cost of chemotherapy for advanced disease is a small proportion of the total cost (<1%). Estimates for cost effectiveness of prophylactic tamoxifen is based on a district health authority population with a 1 million population and 120,000 women aged 45-64. It is assumed that around 7% of women are at increased risk of breast cancer and would be eligible for chemoprevention with tamoxifen. The estimated cost of breast cancer for this population is about 1.5 million per year. The cost of delivering tamoxifen prophylaxis to the eligible population would be around £100 per woman year.

The main adverse effect included is the cost of endometrial cancer (£2,261). At 3 per 10,000, the baseline rate of endometrial cancer is low in the UK compared with the USA. The relative risk of endometrial cancer with prolonged tamoxifen use is insufficient to have a significant effect on overall cost effectiveness.

The cost effectiveness derived from estimating the incidence of breast cancer in a cohort of women taking tamoxifen over 6 years using the results from NSABP P-1

may be between £4,274 and £784.5 per life year gained depending on whether a high cost or low cost scenario is used. This covers the possible effects of long term tamoxifen use on morbidity, the inclusion or exclusion of personal costs to the women themselves and assumes a 5 or 10 year protective effect respectively for tamoxifen in reducing breast cancer risk.

The sensitivity analysis explores alternative means of service delivery including a GP based service and the expenditure assumptions within the research protocol for IBIS. Also included in the sensitivity analysis is the impact of morbidity on cost effectiveness. Earlier work (chapters 4 &5) found no significant differences between the two arms of the trial for morbidity assessed either as rate of hospital use or use of medications. There were however non-significant differences in the rate of use of hospital visits for benign breast disease and for the use of beta blockers which merit further analysis with increasing accrual and duration of the study.

The costs of care set out within the GP led service, in keeping with other forms of chemoprophylaxis such as hormone replacement therapy for osteoporosis, could possibly be reduced from the £410 per woman included here. Lower cost might be achieved if, for example, the level of specialist involvement were targeted only towards problems or difficult cases. Current thinking within IBIS does however suggest that specialist input would be recommended. In general practice the personal costs for the women themselves would be low.

For developing health policy in relation to tamoxifen chemoprophylaxis the level of risk of the target population is clearly of considerable importance in terms of cost effectiveness. For women at very high risk (10-fold risk) the cost effectiveness is around five times lower than for woman at 2 fold increased risk of breast cancer. The eligibility criteria used for entry to the NSABP P-1 and to IBIS provide a useful basis for deciding access to tamoxifen chemoprophylaxis within the NHS since they have achieved a high-risk population in both studies. Developing referral criteria on this basis would provide support for GPs in advising women and ensure cost-effective use of resources available for care and prevention of breast cancer.

Appendix 1: The range of cost effectiveness estimates for alternative costs of service delivery and including or excluding costs of morbidity at either £5 or £43 personal costs per woman.

1. Cost effectiveness for nurse led service (£535/woman) assuming £5 personal cost per woman.

			Morbidity scenario	
Cost (£)	Plus benign breast disease plus beta blockers	Minus benign breast disease minus beta blockers	Plus benign breast disease minus beta blockers	Minus benign breast disease plus beta blockers
Cost of service delivery	53,603,779.9	53,603,779.9	53,603,779.9	53,603,779.9
Morbidity				
benign breast disease	16,081,133.97	16,081,133.97	16,081,133.97	16,081,133.97
beta blockers	107,207.5598	107,207.5598	107,207.5598	107,207.5598
Personal cost				
@£5	2,500,000	2,500,000	2,500,000	2,500,000
Total Cost	72,292,121.43	39,915,438.37	72,077,706.31	40,129,853.49
Savings (breast cancer)	11,931,927.74	11,931,927.74	11,931,927.74	11,931,927.74
Cost per breast cancer prevented	30,874.78	14,313.82	30,765.10	14,423.49

2. Cost effectiveness for GP led service (£410/woman)				
Assuming £5 personal cost per woman.				
Cost (£)				
	Plus benign breast disease plus beta blockers	Minus benign breast disease minus beta blockers	Plus benign breast disease minus beta blockers	Minus benign breast disease plus beta blockers
Cost of service delivery	41,103,779.9	41,103,779.9	41,103,779.9	41,103,779.9
Morbidity				
benign breast disease	16,081,133.97	16,081,133.97	16,081,133.97	16,081,133.97
beta blockers	82,207.5598	107,207.5598	107,207.5598	107,207.5598
Personal cost				
@ £5	2,500,000	2,500,000	2,500,000	2,500,000

Total Cost	59,767,121.43	27,415,438.37	59,577,706.31	27,629,853.49
Savings (breast cancer)	11,931,927.74	11,931,927.74	11,931,927.74	11,931,927.74
Cost per breast cancer	24,468.13	7,919.95	24,371.24	8,029.63
prevented				

3. Cost effectiveness assuming IBIS costs (£200/woman) and £5 personal cost per woman				
Cost				
	Plus benign breast disease plus beta blockers	Minus benign breast disease minus beta blockers	Plus benign breast disease minus beta blockers	Minus benign breast disease plus beta blockers
Cost of service delivery	20,103,779.9	20,103,779.9	20,103,779.9	20,103,779.9
Morbidity				
benign breast disease	16,081,133.97	16,081,133.97	16,081,133.97	16,081,133.97
beta blockers	40,207.56	107,207.56	107,207.56	107,207.56
Personal cost				
@ £5	2,500,000	2,500,000	2,500,000	2,500,000
Total Cost	38,725,121.43	6,415,438.37	38,577,706.31	66,29,853.49
Savings (breast cancer)	11,931,927.74	11,931,927.74	11,931,927.74	11,931,927.74
Cost per breast cancer	13,704.96	-2,821.73	13,629.55	-2,712.06
prevented				

4. Cost effectiveness for nurse led service(£535/woman)				
Assuming £43 personal cost per woman.				
Cost				
	Plus benign breast disease plus beta blockers	Minus benign breast disease minus beta blockers	Plus benign breast disease minus beta blockers	Minus benign breast disease plus beta blockers
Cost of service delivery	53,603,779.9	53,603,779.9	53,603,779.9	53,603,779.9
Morbidity				
benign breast disease	16,081,133.97	16,081,133.97	16,081,133.97	16081,133.97
beta blockers	107,207.56	107,207.56	107,207.56	107,207.56
Personal cost				
@£43	21,600,000	21,600,000	21,600,000	21,600,000

Total Cost	91,392,121.43	59,015,438.37	91,177,706.31	59,229,853.49
Savings (breast cancer)	11,931,927.74	11,931,927.74	11,931,927.74	11,931,927.74
Cost per breast cancer	40,644.60	24,083.64	40,534.92	24,193.312
prevented				

5. Cost effectiveness for IBIS model (£200/woman)				
assuming £43 personal cost per woman.				
Cost				
	Plus benign breast disease plus beta blockers	Minus benign breast disease minus beta blockers	Plus benign breast disease minus beta blockers	Minus benign breast disease plus beta blockers
Cost of service delivery	20,103,779.9	20,103,779.9	20,103,779.9	20,103,779.9
Morbidity				
benign breast disease	16,081,133.97	16,081,133.97	16,081,133.97	16,081,133.97
beta blockers	40,207.56	107,207.56	107,207.56	107,207.56
Personal cost				
@£43	21,600,000	21,600,000	21,600,000	21,600,000
Total Cost	57,825,121.43	25,515,438.37	57,677,706.31	25,729,853.49
Savings (breast cancer)	11,931,927.74	11,931,927.74	11,931,927.74	11,931,927.74
Cost per breast cancer	23,474.78	6,948.09	23,399.37	7,057.76
prevented				

6. Cost effectiveness for GP led service(£410/woman)				
Assuming £0 personal cost per woman.				
Cost				
	Plus benign breast disease plus beta blockers	Minus benign breast disease minus beta blockers	Plus benign breast disease minus beta blockers	Minus benign breast disease plus beta blockers
Cost of service delivery	20,103,779.9	20,103,779.9	20,103,779.9	20,103,779.9
Morbidity				
benign breast disease	16,081,134.0	16,081,134.0	16,081,134.0	16,081,134.0
beta blockers	40,207.6	107,207.6	107,207.6	107,207.6

Personal cost				
£0				
Total Cost	36,225,121.4	3,915,438.4	36,077,706.3	4,129,853.5
Savings (breast cancer)	11,931,927.7	11,931,927.7	11,931,927.7	11,931,927.7
Cost per breast cancer	12,426.2	-4,100.5	12,350.8	-3,990.8
prevented				

Recommendations

1. Where tamoxifen chemoprophylaxis for breast cancer is introduced into routine health care, protocols for ensuring that eligibility criteria are met will be needed in order to maximise cost effectiveness. Consideration should be given to restricting eligibility for tamoxifen chemoprophylaxis to the groups of women eligible for NSABP P1 or IBIS. This would include broadly three main groups of women 1) women with a history of atypical hyperplasia or LCIS 2) a group of women eligible because of a combination of age and family history – following the principle that younger women would need a higher level of family involvement to be risk equivalent and postmenopausal women at high risk for breast cancer who have had a hysterectomy. The priority would be to secure a group of women with at least 3 fold relative risk.

2. The level of specialist support for tamoxifen chemoprophylaxis for breast cancer should be established with the aim of avoiding unnecessary investigations and follow-up. Service delivery in primary care with referral into routine breast services for consultant or specialist nurse advice when needed is feasible given the likely level of demand within health districts and should be fully evaluated..

3. Decisions regarding the availability of mammography screening for women taking tamoxifen will need to be made in the light of findings from research addressing the value of more frequent mammography for women at high risk for breast cancer. Any protocol for service delivery will need to ensure integration with the NHS Breast Screening Programme in order to avoid duplication and wasted resources.

4. Further research is needed to:

- Monitor the long term consequences of tamoxifen use on the general health and morbidity of women. Long term breast cancer adjuvant studies are useful in providing information on the safety of trials for tamoxifen prophylaxis but more detailed studies are needed to assess the effect of long term exposure to tamoxifen for chemoprevention of breast cancer in healthy asymptomatic women. In

addition, small changes in the use of hospital services or prescribed medications for the age group targeted in prevention trials could have a significant impact on the overall cost of tamoxifen chemoprophylaxis because of the potentially large numbers of women involved. The long term impact on vascular symptoms and on benign breast disease in particular is unclear and will require further research to establish fully.

- Further assessments of well being and quality of life are also needed since the women studied here are self selected women and likely to be highly motivated with a positive attitude towards the prospect for chemoprevention.

- Assess whether the reduction in incidence of breast cancer found in the NSABP P-1 study will act to delay the onset of disease or will reduce mortality. The precise duration of the effect after cessation of the period of active intervention with tamoxifen treatment is also uncertain.

- Clarify the impact of age on efficacy of the intervention in order to understand fully the value of chemoprophylaxis for women at high risk for breast cancer by virtue of age.

- In general research on alternative means of preventing mortality and morbidity from breast cancer should be pursued. For example, an understanding of the biological plausibility of casual link between dietary fat and breast cancer discussed in this study cannot exclude the possible importance of diet at key development stages. In particular, the relationship with onset of menarche and early adolescence where the impact of diet on breast carcinogenesis may be profound. A number of randomised controlled trials are underway in the USA although these are focussing only on the recruitment of adult women. Further studies on the use of other chemopreventive agents are also underway.

Conclusions

Findings from this study suggest that the cost effectiveness of tamoxifen chemoprophylaxis for breast cancer could realistically be set in the range between £4,724.0 and £2,596.2 per life year gained with a 5 year duration of protective effect. The upper and lower limits are defined by putting together high or low estimates for key elements of cost. The high cost scenario includes

- A service based on a specialist hospital model at £535 per woman
- The cost of excess morbidity from long term tamoxifen use
- Personal costs to the woman due to clinic visits of £43 per person over the 5 year period of active intervention.

The low cost scenario includes

- A service model based in primary care
- No excess costs due to morbidity arising from tamoxifen use
- Health benefits reducing the cost of general health care in addition to reducing the risk of breast cancer for women taking tamoxifen
- Personal costs to the woman due to clinic visits of £5 per person or less over the 5 year period of active intervention

The study found that the cost of delivering breast cancer chemoprevention per women is relatively low in comparison with many other health care interventions. Yet the overall cost effectiveness is sensitive to a number of factors including the baseline risk of the women and the magnitude and duration of the protective effect. Changing the risk status of eligible women from 2 fold to 5 fold average population risk results in a 50% improvement in the cost effectiveness estimate. For women at moderate or low absolute risk of breast cancer the number who need to take tamoxifen to prevent one breast cancer is relatively high in comparison with the numbers of breast cancers prevented. Even where a high risk population can be successfully targeted a large

proportion of the cost lies in the number of women who need to be treated in order to prevent one breast cancer.

Introducing tamoxifen chemoprophylaxis for breast cancer into the NHS will rely on effective means of targeting women at high risk and of ensuring lowest possible costs of service delivery. Given the small numbers of women who might be eligible for chemoprophylaxis within the average health district it is likely that any increased demand would be absorbed within present breast cancer services or indeed in general practice.

Chemoprevention trials have not been designed to assess whether findings for high risk women can be generalised to all women. The outcome found in the NSABP P1 - of almost 50% reduction in risk of breast cancer is for a population of women at around 3 fold baseline risk. The NSABP P1 trial did however provide evidence that women with a history of LCIS or atypical hyperplasia were more likely to develop invasive cancer than had been previously expected and that tamoxifen chemoprophylaxis could reduce the risk. Introducing tamoxifen chemoprophylaxis into the NHS will require consideration of the appropriate level of service based on criteria for referral and precise assessment of the need for specialist support and the importance of integration with the NHS Breast Screening Programme. Delivering tamoxifen chemoprophylaxis through primary care does however seem feasible. Despite the frequency of visits to clinic settings for women enrolled into IBIS specialist clinical input at consultant level is minimal and mainly focussed on the initial visit. A reduced number of visits to hospital is possible providing the woman has access to her GP for follow up. Referral for mammography could also be reduced to the initial visit. More frequent mammography may be inappropriate for a health intervention targeted towards reducing the risk of breast cancer.

Eligibility for tamoxifen chemoprophylaxis could cover three main groups of women: women with a history of atypical hyperplasia or LCIS, the group of women under 50 with sufficient risk to warrant eligibility to the NSABP P1trial and postmenopausal women at high risk for breast cancer who have had a hysterectomy. Since women in these categories are likely to have an average relative risk of at least 3 fold relative risk these may well be appropriate criteria for targeting women in the UK.

Interest in the possible use of the drug tamoxifen for chemoprophylaxis of breast cancer came about as a result of findings of a 35% reduction in the risk of breast cancer in the contralateral breast for women taking tamoxifen. This could potentially have substantial public health significance if applicable to prevention for women without diagnosed disease - potentially reducing the death rate to around 40 per 100,000 per year preventing more than 5000 deaths per year. Even where a prophylactic application may be verified empirically such a broad scale improvement is unlikely from tamoxifen chemoprophylaxis since the intervention is aimed at high risk women in the age range 40-65 while over 60% of breast cancer deaths are in women aged 65 and over.[6] Moreover costs are highest where the risk status of the women involved is equivalent to that in the general population.

Recent evidence suggest that there is a reverse in the previously rising trend of incidence and mortality from breast cancer in the UK. Analysis of trends in mortality in birth cohorts since the 1930 presented here support the view that the decline is most likely to be due to the assiduous application of effective therapeutic regimen. There may also be a role for changes in the distribution of risk in birth cohorts or period effects. The effect cannot be attributed to the NHS Breast Screening Programme.

Background figures for incidence, with which to compare a preventive intervention, are difficult to ascertain because of the impact of the NHS Breast Screening Programme on the rate for registration of breast cancer. Since the introduction of the NHS Breast Screening Programme the lifetime probability of acquiring breast cancer for a woman aged 30 (with a life expectancy of 83) was 1 in 11 in 1982 and 1 in 9 in 1992. The breast-screening programme was introduced in 1988. Mortality endpoints are most desirable in assessing the efficacy of chemoprevention since the prospect that tamoxifen modifies the rate of or blocks carcinogenesis rather than inhibiting the inset of disease cannot be ruled out. Nevertheless possible effects of chemo prevention in risk reduction, compressing or delaying the development of breast cancer may be beneficial. Cost effectiveness will depend on the duration and magnitude of the effect and the absolute risk reduction in the treated population.

Hitherto, efforts to reduce mortality and morbidity from breast cancer have focussed on secondary prevention through the NHS Breast Screening Programme and treatment of disease through appropriate application of adjuvant therapy. Estimates of the likely reduction in risk of death from breast cancer with chemoprevention have been predicted from adjuvant studies where a review of long term follow up has shown a consistent improvement of around 50% in ten year survival with use of tamoxifen after surgical resection of disease. Consistent with this finding, a recent report from the NSABP Breast Cancer Prevention Trial found a 49% reduction in risk of invasive breast cancer in healthy women taking tamoxifen. This has not been confirmed by the publication of two further preliminary reports from chemoprevention studies. Differences in the study populations may however may be responsible for these contrary findings.

The screening trials have proposed a relative risk reduction in mortality of around 24% - for screened women. Results from international regression analysis for the effect of dietary fat reduction on population mortality from breast cancer suggest a possible 24% reduction with a low fat dietary intervention. A review of epidemiological evidence for the relationship between diet and breast cancer however cannot confirm these findings. Better designed studies are able to control for family history or reproductive risk factors, but none has sufficient heterogeneity in fat intake to detect adequately the effect of a reduction in mortality of anything near the 24% seen in international regression analysis.

This study shows that the cost effectiveness of tamoxifen chemoprophylaxis of breast cancer is within acceptable limits for implementation in comparison with the present programme for care and prevention of breast cancer providing certain conditions are met. For an average district health authority population of 250,000 people with about 100 deaths from breast cancer per year full implementation of effective adjuvant therapy may prevent around 30-40 deaths, the screening programme may prevent 10-15 deaths. For preventive interventions the scope for dietary effects though far from proven may have the potential of saving 20-25 deaths; with tamoxifen chemoprophylaxis targeted only at say the 10% high risk women in the population would prevent only 5-10 deaths.

There are few other studies available with which to compare the validity of the approach used in seeking to understand the likely impact of long term tamoxifen chemoprophylaxis on the changed morbidity experience of women. The use of hospital services is frequently cited in studies of needs assessment as a proxy for morbidity in the population[187, 188, 189] and a linear relationship might be expected. Where the relationship is less than perfect it is possible that the methodology may have underestimated the true impact on morbidity. The study does however review other possible means by which morbidity may have been expressed either through changes in the quality of life of the women involved or through changes in the use of primary care services - reported visits to general practice. Neither of these showed any significant changes in reported morbidity or in decrements in quality of life though attention should be given to this issue in further follow up.

Efforts were made to ensure accuracy and completeness of reports from the women through hand searching of records. Validation of the approach was sought through reference to routine sources of information. In the case of hospital resource use validation of the information on reasons for use of health services including diagnosis and procedures undertaken was sought through comparison with the rate of admissions to hospital by women in the general population reported in the Hospital Episode Statistics. For the rate of use of medications further information with which to validate the approach was sought through comparison with the National Morbidity Survey and through review of data for women of the same age registered with a large general practice.

There were no significant findings in this study to suggest that long term tamoxifen use in the context of chemoprevention affects morbidity. There were no significant differences for women allocated to tamoxifen or placebo in the self reported rate of use of hospital services or use of prescribed medications. Further recruitment to IBIS or indeed detailed analysis of morbidity trends in other prevention studies is needed to explore this further since confirmation of the non significant trend that did emerge in changed use of hospital visits for benign breast disease may change the costs of breast cancer chemoprevention by between 30 and 38%. By contrast, confirmation of a non significant trend of increased use of beta blockers for the relief of menopausal

symptoms as often experienced by women taking tamoxifen would affect the cost by less than 1%.

In terms of the distribution of cost a small number of women do account for a large proportion of the overall costs. This finding suggests that it will be the impact of tamoxifen chemoprophylaxis on increasing or reducing the incidence of high cost procedures, which determines the cost impact from morbidity. Adjuvant studies report that acute toxicity of tamoxifen is low and prolonged exposure in adjuvant studies does not appear to result in adverse effects on coronary heart disease or bone mineral density despite its anti - oestrogenic properties. In fact, where serum levels of lipids and lipoproteins have been monitored tamoxifen appears to have an oestrogenic effect improving the lipid profile. There are concerns about an increase in the relative risk of endometrial cancer for women taking adjuvant tamoxifen. This effect appears to be dose and duration dependent. For women receiving adjuvant tamoxifen at a dose of 20mg per day the relative risk appears to be between two and three fold . Estimates from chemoprevention studies are now as high as a five-fold increase although the absolute numbers are low. The median cumulative dose of tamoxifen needed before diagnosis of endometrial cancer estimated from the Stockholm Trial was 29g. This level would be reached after four years of treatment with a daily intake of 20mg as given in IBIS.

There is both clinical and biochemical evidence of an increased risk of thromboembolic events in women taking tamoxifen. The effect is clearly complex and multifactorial influenced also in adjuvant studies by the presence of disease and the impact of chemotherapy. The relative risk for women taking tamoxifen alone either as an adjuvant therapy or for prophylaxis may be between three and five fold although was less than two for all thromboembolic disease in the NSABP Breast Cancer Prevention Trial. The relative risk appears to increase when tamoxifen is taken in combination with chemotherapy with implications for treatment options; the effect is greater in postmenopausal women.

The impact of long term exposure to tamoxifen on cardiac health may be at least as important as the end point of primary breast cancer reduction. Consistent findings of an effect on lipid lowering may give rise to a relative protective effect of tamoxifen

on mortality from myocardial infarction of around 2.0 though the recent updated overview of randomised trials of adjuvant therapy among women with early breast cancer showed no significant difference in the aggregate of all cardiac or vascular deaths after about five years of tamoxifen. The long term impact on cardiac morbidity in general is unclear and will require further research to establish fully. The precise duration of the effect after cessation of tamoxifen treatment is also uncertain.

The impact of tamoxifen on bone mineral density in postmenopausal women seems to be an increase primarily in the lumbar spine and hip by an annual increment of around 1.5% though this increase appears to occur only during the early years of tamoxifen use. Some evidence also suggests that the protective effect on BMD may be lost after cessation of use and similar effects on radial bones appear doubtful. Larger studies are needed to confirm the reduction in bone mineral density in premenopausal women suggested in results from the Royal Marsden prevention pilot and to assess both the duration of this effect and the clinical significance.

The overall cost for delivering tamoxifen prophylaxis within the context of IBIS is estimated at £1,116 per woman per 5 years. The largest proportion of cost (57%) is in staff time. The cost of Doctor time is the largest element; the amount of time spent by the Doctor explains the difference in cost between the centres. Tests and investigations account for a further 23% of the cost and provision of the drug tamoxifen for 14% of the cost. Costs of administration make up the remainder of the cost (6%).

The main time element in the provision of tamoxifen chemoprophylaxis is in discussing the concept to the women and the protocol for consent to enter the trial . While the time element in 'consenting' woman may translate into time spent discussing the evidence base and side effects of tamoxifen prophylaxis if the approach was adopted in routine practice some savings could be made. Two scenarios for service delivery are used in the cost effectiveness analysis. These are £535 for a specialist nurse led hospital based service or £410 for a service run in general practice. The nurse led service is used as the baseline approach for the model developed in chapter 7 and the GP run service is explored through the sensitivity analysis. Both approaches would rely on minimal input from a consultant surgeon or

equivalent with only 1 visit included for the 5-year period. The frequency of mammography would be a maximum of 3 times in the 5-year period of active intervention. Both scenarios exclude the costs attributable to the research trial particularly the need for annual mammography, the taking and processing of blood and time spent recruiting women to the study.

The costs borne by women using a service for tamoxifen chemoprophylaxis based on women recruited to IBIS range from £20 to £30 per year of recruitment depending on whether time spent travelling to or during clinic visits is excluded or costed at average hourly earnings for women in this age group. This includes both the cost of work lost due to clinic visits, costs of travel to the clinics or other costs associated with clinic visits. Women recruited to IBIS are willing to travel long distances to receive the chance of taking tamoxifen chemoprophylaxis. 75% of journeys are longer than 30 minutes with half of these being over 1 hour. Over 60 % of women sampled reported that they would wish to take tamoxifen at even a low level of absolute benefit (1 death prevented per year); 84% of the women would be happy to travel to a specialist centre to receive tamoxifen. There was no difference in the pattern of use of primary care between the 2 arms of the trial.

Including the personal costs to the women themselves in the cost effectiveness analysis increases the cost by between 1% and 8% depending on whether an allowance is made for the cost of time spent in travelling to or attending clinic visits. Where the service was made available in primary care this cost would be minimal.

Health status of women recruited to IBIS was measured using the SF36. This proved to be a practical and acceptable instrument for use in a postal questionnaire. Responses to the SF36 show that women recruited to IBIS have the same pattern of health as women in the general population across all of the health dimensions including physical functioning, role limitation (includes both physical and emotional), social functioning, pain, mental health energy/fatigue and general health perception. Energy and fatigue has the lowest score for both groups. There is also no significant difference in any of the health dimensions between the 2 arms of the trial. There appear to be no adverse effects on quality of life for women taking long term

tamoxifen prophylaxis and no adjustment for quality of life is needed in assessing cost effectiveness.

The cost effectiveness of tamoxifen chemoprophylaxis can be compared with other means of reducing breast cancer incidence although there are problems of comparability particularly in estimating the savings from the cost of breast cancer prevented. Boer and de Koning [12] published cost effectiveness estimates for the current programme of £25,142 per death prevented and £24,205 or £27,865 for extending the age range to 65 or reducing the interval to two years respectively. The estimates for cost effectiveness of tamoxifen prophylaxis fall below this range providing that the effect of risk reduction translates into a mortality benefit. Further assessment of whether the results for reduction in incidence found in the NSABP P1 represent a delay in the development of cancers or a permanent benefit is also an important priority for further research. Estimates for the cost effectiveness of early treatment for breast cancer to year 10 of between £10,625 ($17,000) per death prevented for women at all ages in the highest risk categories to £31,250 ($50,000) for women at any age at a lower risk of death are substantially more favourable than for breast screening outcomes though may be considered comparable to the range of cost effectiveness reported here for tamoxifen chemoprophylaxis.

There is insufficient information on the present management of women at high risk for breast cancer to compare with the costs estimated for chemoprophylaxis of breast cancer. Bilateral prophylactic mastectomy has been a treatment choice for some women though there are few routine data available to assess the frequency of use of this approach, its survival advantage or cost effectiveness.[13] Annual mammography has also been suggested for women in high-risk categories though there are no data at present to assess the efficacy or cost effectiveness of this approach.

To date no other cost effectiveness studies of breast cancer chemoprevention have been published. Yet a complete understanding of the value of chemoprophylaxis of breast cancer will rely on the impact of long term drug use on morbidity and on the quality of life and the well being of the women as well as the cost of service delivery. Further research is needed to

- Monitor the long term consequences of tamoxifen use on the general health and morbidity of women. Small changes in the use of hospital services or prescribed medications for the age group targeted in prevention trials could have a significant impact on the overall cost of tamoxifen chemoprophylaxis because of the potentially large numbers of women involved.

- Further work is needed to assess whether the effects found in the NSABP P1 study measure a delay in breast cancer mortality rather than prevention.

In general research on alternative means of reducing mortality and morbidity from breast cancer should be pursued. An understanding of the biological plausibility of causal link between dietary fat and breast cancer discussed in this study cannot exclude the possible importance of diet at key development stages. In particular, the relationship with onset of menarche and early adolescence where the impact of diet on breast carcinogenesis may be profound. Further research is needed to address this issue. A number of randomised controlled trials are underway in the USA although these are focussing only on the recruitment of adult women. There are difficulties in undertaking prevention trials because of the concerns raised by ethics committees about the recruitment of healthy women and because of the numbers of women involved.

Long term breast cancer adjuvant studies are useful in providing information on the safety of trials for tamoxifen prophylaxis but more detailed studies are needed to assess the effect of long term exposure to tamoxifen for chemoprevention of breast cancer in healthy asymptomatic women.

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