COUNTING THE COSTS OF CANCER CARE:

BREAST, CERVICAL AND LUNG CANCER IN TRENT

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Abstract

The purpose of this thesis is to explore the theory, practice and application of costing with specific reference to cancer. In part it reviews the theory and guidelines related to costing methods including the recent focus on the analytical techniques used with cost data. In addition it examines how these theories and guidelines are applied in practice, by reviewing the literature on costs and cancer. The empirical research in this thesis applies costing methods to three specific cancer sites; breast, cervix and lung. This analysis provides information on the total burden of these specified cancers in terms of cost to a typical health authority (Trent). It also explores the hypothesis highlighted in previous studies that the cost of cancer increases with the stage of the disease. The final area of contribution for the thesis is in the application of recently suggested analytical techniques for cost data to the breast, cervical and lung cancer data sets; it investigates a number of proposed techniques for the analysis of skewed cost data and methods for data with incomplete patient follow up.

Declaration of authorship

The work presented in this thesis has been composed by the candidate, Jane Wolstenholme. The work has not been submitted in any previous application for a degree.
All quotations have been distinguished by quotation marks and sources of information acknowledged.
Some of the research presented in this thesis has been published in peer reviewed journals.

Published work from thesis:

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Chapter 7:
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Chapter 1

Introduction

1.1 The role of costing in the economic analysis of health care

It is recognized that in order to ensure that the health service maximizes patients' benefits from the limited resources available, a systematic assessment of the costs and consequences of treatments or interventions in health care is required. The tool used for this purpose is known as economic evaluation. Such evaluations explore the relationship between the costs (resources used) and effects (health benefits) for an intervention compared with an alternative strategy. The incremental cost-effectiveness ratio (ICER) reports the difference in mean per patient cost (C) divided by the difference in benefits (E) of the alternatives being assessed:

$$\frac{C_A - C_B}{E_A - E_B} \leq M$$

Where the left-hand side of the above equation is the incremental cost-effectiveness ratio (ICER), and M is equivalent to the maximum amount a decision-maker is willing and able to pay for an extra unit of effectiveness. The first form of economic evaluations of health care tended to be cost-of-illness studies undertaken on a cost-benefit framework(1-6), whereby the benefit side of the equation was estimated to be reduced costs of treatment and reductions in loss of productivity. These cost-of-illness evaluations are similar to cost-benefit evaluations, where the costs of the programme/intervention are compared with the benefits from the programme/intervention to see whether a net benefit exists. Both

these approaches rely on the ability to value both the inputs and outputs in some form of monetary measure. The weakness of the approaches lies in the estimation of monetary values for non-monetary outcomes[1.1]. This weakness led to the development of cost-effectiveness analysis, in which the effects are measured in physical units such as life-years gained or number of cancers detected/ prevented. This approach has been further refined to allow for comparisons across disparate diseases and medical technologies such as rheumatoid arthritis and childhood cancers, by 'quality adjusting' the life years gained. This type of economic evaluation is termed a cost-utility analysis. The central theme pertaining to all these types of evaluations is the cost side of the equation. Thus, the definition, identification, measurement and valuation of costs are central to economic evaluations of health care.

Although costing is central to any type of economic evaluation, until recently there has been little emphasis placed on the methods involved in identifying, measuring, valuing and analysing costs. This relative lack of interest is reflected in guidelines of methodology for economic evaluation in health care(10-12), while other researchers have been more explicit:

"*Although economists are seen as experts on costing by health professionals, the key issue in economic evaluation is the choice of outcome measure.*" (13:279).

Recently there has been a resurgence of interest in the cost side of the equation. Although the attention has focused on the appropriate statistical analysis of cost data(14-19), rather than the unresolved issues of how to value the identified units of resource use.

[1.1] Methods exist for the valuation of non-monetary outcomes in a monetary format; revealed preference (7) and contingent valuation (willingness-to-pay methods) (9).

1.2 Contribution of the thesis

This thesis considers the theory, practice and application of costing. In part it reviews the theory and guidelines of costing methodology and explores the recent focus on the analytical techniques used with cost data. It also aims to determine how these guidelines are applied in practice, by reviewing a sample of published papers that report on cancer costs. Previous reviews of costing methods are limited in number and none report on how the theory and guidelines are translated into practice. This review therefore aims to provide an insight into the strengths and limitations of costing methods outlined in the guidelines and theory and used in practice. The literature review is also used to inform the main part of the thesis, which is devoted to applying costing methods to the disease, cancer. Cancer is an important disease and, for the purpose of costing, exhibits interesting properties.

Despite progress in research providing a better understanding of cancer and as a result improved prognosis of cancer patients being observed over recent decades, malignant disease remains the number two cause of mortality in most industrialized countries (behind cardiovascular disease). It is responsible for approximately a quarter of all deaths in Europe, North America and Japan(20). In terms of morbidity one in three people will develop cancer in their lifetime(21). It is primarily a disease of the elderly, with an incidence rate for those aged 65 years and older being in the region of ten times greater than those aged less than 65 years. The interest with respect to costs and cancer is that cancer imposes a drain on societal resources. This is made up of the medical resources such as personnel, equipment and materials, used in the diagnosis, staging, treatment and follow up care of cancer patients, plus the loss of time and production for the patients and their relatives while receiving or traveling to and from treatment, and any impact

on society due to loss of productivity as a result of morbidity or premature mortality. In this thesis the focus is on the costs of medical resources, in particular, hospital costs.

Researchers often make reference to the medical cost of cancer(22-24), for example:

"*Particularly in the case of cancer, the economic issue is relevant as the costs per case are particularly high,...*" (22:S10)

"*The economic impact of cancer is enormous, with some 5% of health care resources in industrialized countries devoted to its treatment and prevention*"(23:S1).

"*...issues in cancer therapy, which accounts for around 7 per cent of UK health service spending.*" (24).

The first quote from Bonsel and colleagues is typical of many papers written about cost and cancer, in that there is a general acknowledgement that the costs per case are high, but these statements are rarely backed up by actual cost information, which is unsurprising given that few costing studies of cancer have been undertaken. Similarly, the latter quotes state that the costs of cancer is in the region of 5-7 per cent of most countries health service spending, but how useful is this rather out of date information to a health authority or policy maker and how were these figures calculated? More useful information would be estimates of cost related to specific cancer sites, such as lung and colorectal cancer, including data on the constituents (surgery, radiotherapy, chemotherapy, inpatient stays, complications etc.) of these cost estimates. This thesis explores the hospital based treatment costs for three specific cancer sites; breast, cervical and lung. As well as providing information on the cost per case and total cost burden to a typical health

authority, the thesis explores a further hypothesis highlighted in previous studies of costs and cancer(25, 26). One of the interesting properties of cancer with respect to costs is that cancer unless detected and treated is a progressive disease that develops through well-defined stages. These stages are defined according to the spread of the disease upon detection, if no spread is observed, the disease is classified as an early stage cancer, once spread to local, regional or distant parts of the body, the cancer is classified as a late stage disease. The hypothesis to be tested in this thesis is that early detection leads to a reduction in related treatment costs. Two studies have shown that cost is related to the stage of the cancer, and increases with stage of the disease(25, 26), however a UK study of costs of treating colorectal cancer found no positive correlation between stage of cancer and cost of treatment(27). This thesis adds to the literature on the relationship between stage of the disease and treatment costs, and explores the impact in terms of early detection of disease. It also investigates the impact of other variables such as age and gender and smoking status (where applicable) on costs.

The final area of contribution for the thesis is in the application and exploration of recently suggested analytic techniques for cost data. Two problems associated with cost data are explored. Firstly the distribution of cost data tends to display a positive skew. This skew poses problems for using standard statistical tests when comparing differences in mean cost. The second problem involves incomplete follow up of patients over time. This is often encountered when conducting economic analyses alongside trials, due to drop out (attrition), but is also a problem associated with the retrospective collection of resource use data from medical notes. The thesis explores a number of proposed techniques that take account of incomplete follow up.

1.3 Structure of the thesis

Chapter 2 is a systematic review of the literature relating to costing theory, methods and guidelines. The aim of the chapter is to provide a guide to the complexities of cost estimation by answering four key questions:

1) What are costs?
2) Why are we interested in costs?
3) How are costs estimated?
4) How should costs be analysed?

The methods and techniques reported are examined in terms of current accepted conventions, current debatable issues and areas of methodological evolution requiring further evidence.

Chapter 3 follows from the review of the literature on the theory, methods and guidelines by exploring their applications in practice. This review of costing in practice is restricted to cancer and its treatment. The detailed review identifies areas of imbalance between the methods suggested by guidelines and methods used in practice. Along with the review reported in chapter 2, chapter 3 provides a basis for the design of the empirical work conducted in the remaining chapters.

Chapter 4 details the background and methods related to the three core costing chapters that follow. It provides information on the national estimates of cancer incidence and mortality and includes a general description of cancer, its usual treatment patterns and staging procedures and definitions. Details of the process of

data collection are reported along with information on the geographical region and hospitals used for this purpose.

Chapters 5-7 report on the empirical estimation and analysis of breast, cervical and lung cancer costs respectively. All three chapters are identical in structure. They introduce the specified cancer in terms of mortality and morbidity; details from published sources on the diagnostic procedures and treatments are also discussed. The empirical section consists of information on the patient samples, unit costs, resource utilization and total cost estimates. Further analysis by stage, age, and other variables are examined. All three chapters include a comparison of the cost estimates with the results from other costing studies for the same cancer site. In addition, chapter 5 attempts a detailed evaluation of the impact of the national breast-screening programme using the cost results.

Chapter 8 considers the appropriate statistical analysis of the breast, cervical and lung cancer cost data. Cost data are invariably skewed, which causes problems for using parametric statistical tests. The chapter explores a number of methods used by statisticians and proposed by a few health economists to overcome this problem, including, the removal of outliers, transformation of the data, nonparametric statistics and bootstrapping and re-estimates the data used in chapters 5-7.

Chapter 9 explores the analysis of costs where data are censored. Censored cost data occurs where the end point of interest has not been observed for a particular individual/patient. Several techniques have been proposed in the literature that aim to adjust for any censored data when estimating the average total cost. These range

from ignoring the issue of censoring altogether to estimating costs based on only those with complete cost histories to using a combination of cost and Kaplan-Meier survival estimates that takes account of any censoring. The chapter reports on the results for the breast and cervical cancer data using the proposed techniques.

Chapter 10 provides a discussion of the findings of the thesis in relation to:

1) the theoretical considerations outlined in chapter 2,

and

2) the policy implications for the health service.

Chapter 11 draws together the conclusions of the thesis, with particular consideration given to its contribution and ideas for future work.

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Chapter 2

Estimating Costs - Methodology Review.

2.1 Introduction

This chapter aims to take the reader through the complexities of cost estimation by answering four questions:

1) What are costs?

2) Why, as health economists are we interested in costs?

3) How are costs estimated?

4) How should costs be analysed?

In responding to these questions the appropriate literature was searched and reviewed. The review has been split into two components; firstly a review of published guidelines to costing, and secondly a review of costing methods in practice. These two components of the review are necessary as the published guidelines to costing purely highlight the theoretical 'dos' and 'do nots' of costing with little or no evidence of practice (discussed in this chapter). Whereas the published studies highlight the realities involved in costing procedures (the findings of which are reported and discussed in chapter 3). The first two questions are answered relatively simply with a description of the theoretical underpinnings of cost estimation. However, the last two questions provide scope for detailed and lengthy responses, as the estimation and analysis of cost data has limited standardised methodology, and can be (and is) undertaken in a number of different ways. In fact, the complexities of cost estimation are generally understated by

analysts engaged in economic evaluations. In published technical papers relating to methodological issues in economic evaluations, there tends to be less emphasis on the problems associated with cost estimation compared with those relating to benefits measurement. Moreover, in published economic evaluations it is usually difficult to determine how the final cost estimates are derived. Little explanation is usually given of how the resources are identified and valued, let alone any basic description of what resources are included in the cost estimation.

In answering the questions on estimation and analysis of costs the chapter is structured so that the key costing processes and methodologies are introduced and discussed in the order that one would think about and undertake in practice. It is noticeable that some of these methods for costing have reached consensus, whereas others have been debated and remain unresolved and there have also been new areas of methodological research where ideas are still evolving and further research is required. The discussion part of the chapter examines the methods in terms of:

1) Current accepted conventions
2) Current unresolved/debatable issues
3) Areas of methodological evolution, where further empirical research is required.

2.2 Literature Search - materials and methods

Before any analysis of the cost of cancer could be undertaken, there was a need to understand the costing process. This involved searching for any literature that had been published on the concept of cost and its estimation. The guidance to costing

reported in this chapter was obtained from a number of literary sources procured from a search of the literature conducted in the following manner:

- library catalogue searches for books on economic evaluation and costing
- Medline, BIDS, EMBASE and EconLit searches using search terms 'economic eval*', 'cost', and 'cost-effect*' as key terms in the title or abstract
- internet search of health economics and related sites

  http://www.healtheconomics.com/

  http://www.oheschools.org/

  http://www.york.ac.uk/inst/che/welcome.htm

  http://http1.brunel.ac.uk:8080/departments/herg/home.html

  http://www.shef.ac.uk/uni/academic/R-Z/scharr/

  http://www.abdn.ac.uk/heru/

  http://www.ccohta.ca/

  http://www.york.ac.uk/inst/crd/

  http://www.hta.nhsweb.nhs.uk/
- recommendations from colleagues working in the health economics field, particularly for any grey literature on costing methodology or country specific guidelines.
- relevant books and papers referenced in any of the previously identified literature.

The only exclusion criterion used was that the text should be in English language.

This literature search resulted in a substantial number of relevant articles, reports and textbooks; these are displayed in Table 1. The literature in Table 1 has been organised chronologically according to year of publication. All these publications provide information on the methods, issues and guidance related to the costing process. The review of this literature also provides a background to the evolution

of costing conventions. The costing literature in the 1960s, 1970s and early 1980s focused on the methods used for estimating the cost-of-illness of diseases, however very little was written on the methods during this period. The late 1980s and early 1990s saw an explosion in papers and textbooks aimed at giving guidance on the costing process. However, this tended to be guidance on the theory of costing in line with economic beliefs, hence discussions about direct and indirect costs, opportunity costs, marginal and average costs, study perspective, discounting, how to cost capital and how to deal with overheads. Little information was given on the practical aspects involved in costing(1, 2) and no information was given on how the costs should be analysed or reported. The list of literature in Table 2.1 shows that throughout the 1990's there has been an evolution of ideas and methods related to the practice of costing. This includes an exploration into the practical aspects of costing productivity losses(3-6), and whether they should be included in the total cost estimate for the purpose of a cost-effectiveness ratio(7, 8), the methods involved in costing informal care(9, 10), techniques to reduce the burden of data collection(11, 12), possible methods for dealing with missing cost data(13-15), and issues in the analysis of cost data(16-22). These key issues are outlined below and are explored in greater detail throughout this chapter.

2.2.1 Key areas in the process of cost estimation

- The theoretical basis of cost estimation.
- Process of identification of important cost-generating events to be collected; literature, previous studies, experts' advice etc.
- Process of the measurement of resource-use; questionnaires, patients' medical records, pre-collected database, Delphi panel, trial database, prospective or retrospective measurement.

- Process of valuation of resource-use; source of unit cost data (finance department, published studies, cost estimation), adjustment of baseline price, currency.
- Sample size
- Time-horizon
- Discounting
- Analysis and presentation of cost estimates
- Sensitivity analysis
- Cost estimation with missing data
- Costing alongside censored data

Table 2.1 Methods, issues and guidelines related to costing – Literature search

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2.3 What are costs and why, as health economists are we interested in costs?

"Costing healthcare services is imperative, as money is a limiting resource that always will be taken into account. Studies of health care costs serve as an aid to political and administrative decision making..." Gyldmark(23) (1995:964).

The concept of cost used by economists provides a definition of the term 'cost' as used by health economists when undertaking an economic evaluation. The underlying concept is known as *opportunity cost.* This concept is the foundation for all economic thought, and is based on two prior principles; scarcity and choice. Scarcity exists in all types of society, however abundant the resources in society the individuals in society will always want to consume more goods and services than can be produced from those resources. It is therefore necessary to make a choice among the alternative uses to which the resources could be put. It is inevitable that opportunities to use resources in some activities will be foregone. The economists' term for costs expressed in terms of foregone alternatives is opportunity cost. These principles of scarcity and choice hold in the health care sector, where there are not enough resources to meet the needs or wants of the patients/consumers. Changing demographic patterns and expensive new technology (e.g. hi-tech medicine) provokes the scarcity of health care resources. Therefore choices between alternative interventions or programmes have to be made, and they should be measured and valued in terms of their opportunity cost.

Johannesson (1996) uses the term cost to reflect the opportunity cost in terms of resource consequences of a treatment. The resource consequences are defined as the effect on the consumption of goods and services of a health care programme and the consumption of leisure(24). The estimation of costs is central

to all economic analyses of health care technologies. In essence, costs are the product of the quantification of the resources that are consumed and their respective unit costs. Resource use is the general term for the resources consumed due to a particular health care intervention and is the underlying driver of cost. Examples of resource-use items include outpatient visits, inpatient stays, use of particular equipment for example colonoscopy, medical personnel time. These resource use items and therefore costs can be measured on a patient-specific (stochastic) basis i.e. they vary from patient to patient, or a non-patient specific (deterministic) basis, i.e. they stay the same for each patient. Ideally, resource use and therefore costs should be measured on a stochastic basis (as I will argue later in this chapter) to allow a thorough statistical analysis to be undertaken.

2.4 How are costs estimated?

This section examines what influences the choice of costs to be included in a study and describes the various types of costs that can be measured and valued. It explores the process of identification of cost-generating events, the measurement of these events, the process of valuing cost-generating events and issues relating to costing such as discounting, presenting and analysing cost data.

2.4.1 Factors influencing the choice of costs for inclusion in the study.

Different factors affect the choice of costs to be included in a study. These are discussed below.

Perspective

The perspective or viewpoint of an economic analysis influences the choice of costs to include (25-27). This perspective is partly dependent on the target audience. Perspectives range from the very narrow viewpoints of the patient or clinician, to the intermediary viewpoints of purchaser, decision-maker, health authority, provider unit or government, to the much wider perspective of society as a whole. The costs which a patient incurs when a treatment decision is made - such as transport costs to attend a clinic, lost earnings or child-care costs - are very different from those incurred by the National Health Service (NHS). Similarly only the societal perspective takes account of any costs associated with production loss. The societal approach relies on the collection and valuation of all costs, regardless of who incurs them. The societal approach has been recommended as the standard perspective for costing, as it allows the analysis to be carried out on a number of viewpoints (28-30).

For economic studies of dementia the choice of perspective is particularly important. For example, a policy of home support for people with dementia may reduce hospital costs (NHS) and institutional care costs (social services and patients) but increase the burden of informal care provided by relatives. This process of cost-shifting may transfer costs from one sector/budget to another, but may not reduce the total cost to society as a whole. Therefore when evaluating these types of programmes, care has to be taken to take a broad societal perspective which includes the costs incurred by non-health care sectors such as social services and unpaid caregivers.

Quantitative importance

Some authors have argued that the decision regarding which costs to include in the analysis will depend on their respective quantitative importance, in other words their impact on the total cost and cost-effectiveness result. Some studies have therefore omitted certain cost-generating events arguing that they have little impact on the final result. This is frequently seen in trials where common resource use exists between two arms of a clinical trial. These cost-generating events are excluded from the analysis with the justification that they will have no effect on the final decision making process. Schulman and colleagues (1996) decided to omit the collection of information on blood tests from their study, previous data had shown that even though they were frequently performed they were also of significantly low cost so as to only amount to 1.8% of the total cost(31). However, disregarding cost-generating events on the basis of insignificant quantitative importance or commonality between trial arms may lead to a biased decision-making process. This is because comparisons of cost and cost-effectiveness with other disparate health care technologies may well have to be made outside the initial comparison. Moreover, it is difficult to predict ex-ante which cost-generating events will have a significant impact on the total cost calculation.

Time horizon

The time horizon is defined as the period of time for which the cost-generating events are identified and measured. It is determined by the nature of the study; if prospective and alongside a trial it may be for the length of the trial, if retrospective it will be dependent on whether databases or medical records still exist (32). It may also be dependent on the period of time for which the decision-maker has an

interest. In most cases the decision-makers period of interest will be longer than the availability of the cost-generating event data. This is due to the fact that patient resource-use often continues long after the trial or study period has been terminated. An example of this is with breast cancer cases that may incur resource-use for follow up and recurrences for up to twenty years following initial diagnosis. A long-run perspective has therefore been recommended(30). This requirement for a long-term perspective is reinforced by the fact that a disproportionate amount of resource-use is consumed near death(33). Therefore by limiting the cost analysis to a fixed time period bias may be introduced into any comparison of costs(34). Although it has been recommended that the time horizon for cost analysis should be from a long-run perspective, financial and data-availability constraints exist. Thus rather than collecting data over a long period of time, modelling results beyond a constrained time-horizon has been suggested(14, 15, 35, 36).

Attributable costs

Another area that may determine cost inclusion or exclusion is whether the cost can be defined as being attributable to the intervention or disease being analysed. Of course, it is not easy to specify whether the costs are attributable or not, and can in some instances be a rather arbitrary exercise. One method would be to collect information on all health care resource-use, including the resources used for treating co-morbid conditions. By including all the health care resources consumed, any possible exclusions of unexpected disease or intervention cost-generating events will be avoided, however it may upwardly bias the cost results by including non-related health care costs. This bias could be avoided by asking a panel of experts to decide what cost-generating events are attributable to the

disease in question. Jonsson and Weinstein (1997) when discussing the design of the economic evaluation for the GUSTO IIb trial stated that they opted to limit the scope of resource use collection to those related to coronary heart disease and its treatment, arguing that:

"...the risk is that a few patients with catastrophic episodes of <u>unrelated</u> resource use (e.g. prolonged psychiatric hospitalizations) could swamp the main effect of the intervention." (37:51).

Feasibility

Although it has been argued that the ease of measurement should not influence what costs should be included(30), the final and probably the most powerful factor determining the choice of which costs to include in practice, is feasibility. Time and financial constraints have the greatest influence on what cost data are collected. When data collection is prospective and alongside a trial, time constraints can be a problem for the researchers who have been appointed the task of filling in the resource use questionnaires. In busy outpatient wards research nurses may not have time and subsequently forget to fill in such questionnaires. Accessing all relevant cost-generating events may also be a time-consuming task in cases of retrospective analysis. For direct medical resource use, hospital and GP medical notes have to be obtained and the appropriate information abstracted. As well as being a lengthy task, problems of missing data may arise when pages within the medical notes or the medical notes themselves cannot be traced. It might be thought that routinely collected databases such as cancer registries could be a cheap and time-efficient way to obtain resource use information. However, in practice such databases were initially constructed for other uses and invariably do not

contain all the information required. Access to patients or low response rates can be a problem when administering a questionnaire to assess patient costs such as time, travel and productivity loss. The U.S. records considerable amounts of data regarding health care costs. Medical and non-medical expenditures are included in the National Health accounts, published by the Health Care Financing Administration(38). Short stay hospital episodes are recorded in the National Hospital Discharge Survey by the National Center for Health Statistics (NCHS), and expenses per patient day can be obtained from the annual survey of the American Hospital Association. The National Ambulatory Care Survey conducted by the NCHS keeps records of outpatient care costs. The cost of physicians can be obtained from the physicians' charges documented in the American Medical Association's annual report on physician practice(39). Unfortunately records of data regarding medical resource use and cost in the UK are not so readily available, and even when they are, they are usually outdated or incomplete. The feasibility and practicability of a study therefore conflicts with the theoretical basis of cost identification, measurement and evaluation. However, the aim should be to get the best available data with the recognition of limitations such as time, financial and data constraints.

2.4.2 Which costs?

An overview of the types of costs to be considered for inclusion is provided below. It is useful to consider these costs under the headings of direct health care costs, direct non-health care costs, informal care costs, and productivity costs.

Direct health care costs

Direct health care costs are defined as the 'organizing and operating costs within the health care sector'(25), including the cost of diagnosis, treatment,

rehabilitation, therapeutic and continuing care, terminal care and prevention. They include variable costs such as staff time, general practitioner (GP) services, drugs and other medical supplies, and fixed costs such as medical equipment, building use and overheads such as laundry, electricity, portering etc. They also include number of inpatient bed days, outpatient visits, clinic visits, and general practitioner and nurse visits.

These costs include the cost associated with an intervention, such as a course of drugs or surgical procedure, the costs of treating any adverse events, and the costs of complications arising from the condition, which may be reduced as a result of that intervention.

Some economists have also argued that, where an intervention extends life expectancy, the resulting future use of health care for any reason should also be included. For example, Weinstein *et al.* argue that,

"....if treatment results in a prolonged life because a condition has been cured or early disease has been avoided, then the cost of treating later disease that would not otherwise have arisen must be considered." (40: 240)

However, other analysts have countered this(41), suggesting that,

"...if the purpose of the analysis is to determine whether the programme is a good investment, only the costs of the preventive program should be counted. Added years of life involve added expenditures to food, clothes and housing as well as medical care. None... is relevant to deciding whether the program is a good investment..." (41:35-36).

In the face of this lack of consensus, most studies at present include future related health care costs but exclude unrelated future health care costs from their analysis(42-44).

Direct non-health care costs

Direct non-health care costs may include the costs of care to other agencies such as social service departments providing day care or home helps, and the out of pocket costs incurred by the patient, relatives and friends, for example in making home adaptations, buying over the counter medications, or traveling to and from hospitals or surgeries for treatment and incurring train, bus or taxi fares, petrol costs and parking fees. Patients' time costs are calculated as the opportunity cost of having to take time-off work or from normal activities to attend treatment. They are particularly important in screening programmes, where if the opportunity cost is perceived to be too high it may deter attendance(45-48).

Informal care costs

Informal care costs consist primarily of the time provided by relatives and friends in caring for someone whose condition impairs their independence. All evidence indicates that the volume of time thus provided is very substantial, but for economists the problem lies in trying to place a valuation on it. The approach typically adopted has been to assess the opportunity costs of informal care: if informal care was not provided in this way, what would the informal carer be doing instead, and what care would the patient receive instead? However, this raises some difficult issues: informal carers are often the elderly partners of elderly patients, and it may be hard to define and measure what they would otherwise be doing, and harder still to place a value on this; similarly, while some of the time provided by informal carers might otherwise be provided by formal carers, it seems unlikely that substitution could occur except at the margin.

Productivity costs

Productivity costs of disease may occur as a result of reduced productivity at work; absence from work; disability, and premature mortality attributable to the disease of interest(49). Several studies have debated the issue surrounding the measurement of productivity costs (3-8, 50-53). Koopmanschap and colleagues, (1995) argue that productivity costs are only relevant where the disease or intervention brings about significant changes in productivity. They have contested the idea that illness and absenteeism directly affects production and have put forward the idea of *friction* costs. Even if patients take time off work, actual production may not be affected because other workers can take on the patient's work in the short term, or because the patient makes up lost production on return to work. In the long run, if the patient is unable to return to work, another employee will replace them, and so the cost to society in terms of lost production is close to zero. However, this argument is very much dependent on the perspective of the analysis. When a patient perspective is taken, productivity loss to the patient due to absenteeism or the inability to continue working and carrying out every day activities may well be a cost, depending on the patient's employment conditions and loss of earnings during sickness absence.

Others have argued that the measures used to value productivity costs are unreliable and unrealistic and therefore productivity costs should be excluded from the analysis. Gerard and Mooney, (1993) have proposed that, since the outcome measures in economic evaluations are health specific, the opportunity cost of resources should be defined in terms of health and therefore productivity costs should be excluded(54). However, Meltzer, (1997) has argued that, if the health

care budget has to compete with other public sector budgets to maximize utility, future productivity and consumption costs need to be included.

Ethical reasons for excluding productivity costs from economic evaluations are also sometimes invoked: for example, it is argued that their inclusion will mean the allocation of resources in favour of those of productive age, biasing against the economically inactive and elderly. However, the ethical arguments are not clear-cut: resource allocation decisions do sometimes explicitly take into account the productive potential of individuals, both in health care treatment decisions and in other areas such as court settlements in personal injury cases.

Even if the debate as to whether productivity costs should be included could be resolved, and a decision made as to how to value these productivity costs, there remains a debate as to whether they should be treated as a cost (the numerator in a cost-effectiveness ratio (CER)), or a health effect (the denominator of the CER)(7, 8). Luce, Manning, Siegel and Lipscomb (1996) argue that rather than monetizing these productivity costs and placing them in the numerator of the equation they should be incorporated in the denominator in the form of a QALY estimate(30). The full impact of morbidity is encapsulated in the QALY measure. Similarly any impact on changes in life expectancy is included in the denominator of a cost-effectiveness ratio in the form of life years or QALY's. If the analyst feels that these productivity costs are important, they should present them separately. Any inclusion of these costs in the overall cost measure may result in double counting. An example of this form of double counting could easily have occurred in this thesis. For example, in chapter 4, the cost of the disease process of breast cancer has been estimated, enabling a cost-effectiveness analysis of screening for breast cancer to be undertaken. If the productivity costs relating to breast cancer had been included in

the numeraire of the cost-effectiveness analysis this would have resulted in a biased result due to double counting of the morbidity and mortality costs. The impact on life years and quality adjusted life years were included in the denominator.

2.4.3 Identification of cost-generating events

Although the literature has described the types of costs available for inclusion in the analysis and the factors influencing which costs to include, it rarely specifies how to identify the events that generate these costs. Detailed identification of the costs requires knowledge of the different care pathways for the particular disease or intervention under scrutiny. This can be obtained from a number of different sources.

a) literature on specific diseases/illness or interventions and treatments.

b) previous studies may highlight the parameters which are the main determinants of cost.

c) clinicians and experts' advice on treatment and care for particular diseases.

d) pilot studies using a small sample of medical notes where patients are known to have the disease or have had the intervention in question.

e) trial or routinely collected databases.

f) observations of practice.

If the key cost generating events can be identified in advance, time and money will be saved by collecting data only on these events. It will also limit any burden placed on the patients themselves if questionnaires are required. Knapp & Beecham (1993) and Whynes & Walker (1995) have presented two studies identifying key cost-generating events in mental health care and cancer care respectively(11, 12). In the study of mental health a list of 21 cost items was reduced to 5, which still

accounted for 94% of the total cost. Whereas in the study of colorectal cancer an initial list of 14 cost-generating items was reduced to four, which still accounted for 95% of total cost. However it remains difficult to predict these key cost generating events *ex ante*. Moreover, since the patient variation in total average cost was wide, simply looking at a reduced list of cost generating events conceals the important cost variation between patients(12).

2.4.4 Measuring Resource Use

When the cost-generating events have been recognised and identified they have to be measured and quantified in some format.

Direct health care costs

Direct health care resource-use is usually measured in physical units, for example, number of outpatient/GP/inpatient visits, number of days spent in hospital, staff time, dosage of drugs administered, time spent in an operating theatre, length of inpatient stay. The resource use can be measured at varying degrees of detail. This ranges from the most basic to the most detailed form of costing described by Gold *et al.*, (1996) as 'gross costing' and 'micro costing'(30). Gross costing measures the resource use at an aggregated level then multiplying by the appropriate unit cost. For example, the cost of an inpatient stay can be estimated by measuring the number of inpatient days and multiplying this by the unit cost. Micro costing involves breaking down the hospital stay into its resource components, such as staff time, equipment used, ward space used, overheads such as electricity, portering and laundry and multiplying these measures by their corresponding unit costs. This requires information on staff earnings, the replacement cost of equipment with allowance for depreciation, the replacement cost of ward space and

hospital overhead costs provided by the finance department. It may also be necessary to consider the time spent by nursing or medical staff with specific patients, if the level of dependency of patients is relevant to the study.

Luce and Elixhauser (1990) illustrate the varying levels of detail that can be involved in measuring cost-generating events pointing out that this process can be either 'fairly crude' or 'painstakingly detailed'(26). They cite two studies, one which employed very crude methods to assess the change in health care resources brought about by changes in use of cholesterol lowering drugs(55). The study involved estimating the average treatment process by asking clinicians and consulting the medical literature. The other study used a very detailed time and motion survey to assess the resource implications of changing the methods for administering antibiotics in secondary care(56).

Direct non-health care costs

The measurement of direct non-health care costs such as time and travel costs and out of pocket payments made by the patient and their family/carers, is usually achieved by administering questionnaires to patients or carers(45, 47, 48). The study by Frew and colleagues (1999) collected information from patients attending a screening clinic. Information supplied included modes of transport, out of pocket expenses (fares and car-parking), time spent travelling and in the clinic, activities forgone owing to attendance, details of companions and sociodemographic characteristics. Together these data were sufficient to estimate the time and travel costs incurred by individuals attending a screening clinic for colorectal cancer.

The measurement issues relating to costs pertaining to other public sector budgets have been explored by researchers at the PSSRU (Personal Social Services Research Unit, University of Kent) and CEMH (Centre for the Economics of

Mental Health), leading to the development of a questionnaire to abstract cost information: the 'Client Service Receipt Questionnaire' (CSRI)(1, 57).

Informal care

In collecting information on caregivers' time, techniques such as direct observation, retrospective estimation and diary keeping are used. Standardised instruments have been developed for the collection of information on the resource usage of informal care in studies of dementia, for example, the Caregiver Activities Time Survey (CATS)(58, 59), the Caregiver Activity Survey (CAS)(60) and the Resource Utilization in Dementia (RUD)(61). Measurement of informal care has been discussed in detail elsewhere(9).

Productivity costs

The measurement of the impact of illness of productivity has been well documented(50). A questionnaire, 'the Health and Labor Questionnaire' (HLQ), has been designed to collect data on the relationship between illness, treatment and performance at work(62). The HLQ consists of four modules aimed at collecting data on absence from work, reduced productivity, unpaid labour production and labour related problems. It is currently available in Dutch and English.

2.4.5 Valuing Resource Use Measurement

Direct health care costs

According to economic theory, the true cost in any economic analysis is the opportunity cost. In practice, however, this is difficult to estimate and market prices are generally accepted as approximations to opportunity costs. The valuation of resource-use literally means multiplying the quantity of resource use by a unit cost. The valuation is dependent on the form of measurement, whether

micro or gross costing, which in turn is dependent on what question is being asked, data availability and time constraints. If the question is 'what is the current cost to our region of providing cancer?' short-run average costs can be used, this cost is the total cost of providing the programme divided by the total units produced. However, if the question is 'what is the cost of extending the breast cancer screening programme to women aged 65-69?' marginal costs are required. Costing a programme that involves a change in services requires information on marginal costs. The marginal cost is the cost incurred by using one unit more or one unit less of an intervention or programme. Neuhauser and Lewicki highlighted the importance of looking at the costs at the margin. In their study on the stool guaiac used for the screening of colonic cancer they report how the use of the average cost may be misleading. The average cost of detecting colonic cancer by a single stool test was found to be $1,175, if six tests were conducted on the same patient the average cost increased to only $2,451(63). However the marginal costs for the first and sixth test were $1,175 and $47,107,214. Other studies have shown a marked difference in results from calculating average and marginal costs(64-66). The terms marginal and incremental cost have often been used synonymously(67). Johnston and Brown (2000) use the term incremental cost when comparing different mammographic reading policies for breast cancer screening. However this complies with the distinction that has been made by UK researchers who state that:

"... the appropriate incremental comparisons for cost-effectiveness are sometimes comparisons between entirely different programs and sometimes comparisons between different levels of intensity within the same program. Only the latter fits

the usual definition of marginal. In this way, incremental is a broader term, which includes marginal..." (68:78-79).

However, the argument above relates to cost-effectiveness ratios, in all the examples reported the authors have used marginal or incremental analysis of average costs.

Micro costing involves estimating a unit cost for each level of resource use measured, for example, unit costs are required for staff time, capital (equipment and land), consumables (radiography film, chest drains, drugs, etc.), overheads etc. If resource use has been measured using the gross costing approach, then the unit cost (per diem cost) will include all capital, overhead and staff costs(69, 70). In practice, unit costs are obtained from a variety of sources. They can be estimated in every minute detail by collecting the following data and information.

a) staff time and salaries available from personnel departments or pay review bodies(71, 72).

b) equipment and its useful lifetime, replacement costs and maintenance costs (from the supplier or hospital finance department).

c) land, buildings, theatre and ward space from the finance department (see appendix 2.1 for details on costing capital)

d) overheads for example, portering, general administration, electricity, cleaning, catering and laundry by assessing time, salaries, and actual market cost (hospital finance and accounts departments).

For the more aggregated costing methods, costs used in previously published studies, or more formalized published cost information (for example, PSSRU estimated unit costs(73). Unit costs for drugs can be proxied using the price quoted in the British National Formulary (BNF) and Monthly Index of Medical

Specialities (MIMS)(74, 75). The personnel, accounts and finance departments of hospitals can also offer a source of unit cost data.

'Costing for contracts' and 'reference costs'

Since 1994, Hospital Trusts in England and Wales have been required to undertake a programme of costing activity(76). This came about due to government recognition that a lack of valid and comparable cost data in the NHS was hindering the contracting process in the internal market. They set up a National Steering Group on costing standards by the National Health Service Management Executive. This Group argued that costs should be analysed on a defined standardized sub-speciality level; the healthcare resource group (HRG), and that they should include all fixed, semi-fixed and variable costs. The timetable for implementation required all acute providers to cost HRGs in at least one of three specialities (gynaecology, ophthalmology and orthopaedics) for the financial year 1994-95. The idea was to then expand this programme so that HRGs across all specialities would be costed by 1997-98 and beyond(77). Up to 1997 only two regions (Northern and Yorkshire and North West) made their cost data from all their trusts publicly available.

Costing for contracts was superseded by the introduction of NHS Reference Costs. This idea was heralded in the White Paper, '*The New NHS: Modern Dependable*'(78) with the intention that they will provide information on the efficiency of the hospital sector. The costing process is analogous to that outlined in Costing for Contracts with costs according to HRGs, with the key difference being that all costs will be accessible to the public through the annual publication of the *National Schedule of Reference Costs*(79). The following quote illustrates the policy:

"The Government will develop a national schedule of 'reference costs' which will itemise what individual treatments across the NHS cost. By requiring NHS Trusts to publish and benchmark their own costs on the same basis, the new arrangements will give Health Authorities, Primary Care Groups and the NHS Executive a strong lever with which to tackle inefficiency." (79:19)

November 1998 saw the first schedule of reference costs for 1997/1998 published and provided on the internet: (http://www.doh.gov.nhsexec/refcosts.htm). Detailed information was provided on 536 surgical procedures covering almost 5 million episodes of care across all 249 Trusts. This first publication only covered surgical activity, but the plan is to extend the focus to capture all NHS activity.

Reference costs have been criticised over a number of issues(80, 81). There are problems with the use of finished consultant episodes (FCEs) for specifying HRGs as they have inconsistent definitions across hospital Trusts. For example one Trust may count a transfer from surgery and a surgical ward to a medical ward for continuation of stay and observation as two separate FCEs while another hospital may count this as one FCE. Another problem is that atypical episodes (those where length of stay was above the maximum normally expected for the HRG) have been deleted for the purpose of comparison across Trusts as an indicator of efficiency. This process is known as trimming, and for the 1997/98 National Reference Cost Index excluded 13 per cent of total surgery costs. A final problem of specific note to health economists who use the data for their own costing purposes is that the costs are reported in terms of short-run average costs rather than marginal costs.

Direct non-health care costs

For direct non-health care costs such as patient travel, the measurement is in miles travelled and this can be equated with the Automobile Association mileage rate if private transport was used, along with the charges for car parking at the hospital. If bus, taxi or train were used the actual market price i.e. the fare can be used to value the travel cost(45, 47, 48).

Informal care costs

Two techniques have been used for valuing caregivers' time. The first is the opportunity cost approach which estimates the opportunity cost of foregone activities using the market wage rate as a proxy value for work time and leisure time foregone. The second approach is the replacement cost approach, which uses an imputed value for unpaid caregiver of the national wage for similar care provided in the market place.

Productivity costs

The most influential and widely debated approach for calculating benefits of improvements in health care in the form of increased production, is the human capital approach(82-84). The focus of the human capital approach is on the economic consequences of the disease and is embedded in the theory of marginal productivity, with the assumption that earnings reflect productivity. In practice, if productivity costs are included at all, the typical approach would be to attach an average earnings figure to the estimated time lost.

2.4.6 Data collection

The major determinant as to whether cost-generating events can be measured and valued is whether the data are available. Data collection can either be patient-

specific or non-patient specific, and can be collected prospectively (collected when the event occurs) or retrospectively (collected after the event has occurred). However other important areas related to data collection need to be ascertained before any data collection can take place.

Sampling and sample size

It may not be necessary to collect data from all the patients with the disease or those undergoing the intervention in question. Resource use data can be collected using a random sub-sample of patients. However, care has to be taken to weigh up the pros and cons of sampling. On the 'pro' side it reduces the time and financial burden on the researcher and does not overburden patients with data collection. On the 'con' side, the results might be sensitive to the chosen sample, and it is necessary to assess the bias in the results from a smaller sample, thus sample size determination is an important consideration. However, calculations of sample size based on detecting an economic difference e.g. cost or outcomes are not common, as most studies base their sample sizes on detection of differences in clinical outcome(85). However it has been suggested that consideration of the ability to detect economic differences should be made, this involves specifying the minimum difference in resource use, cost or cost-effectiveness which is considered quantitatively important(86, 87). Drummond and O'Brien (1993) and Torgerson *et al.* (1995) argue that there is no consensus on defining the difference(87, 88). There is also a problem in estimating the sample size required for cost-effectiveness analysis in that there are two outcomes of interest, cost and economic outcomes. Briggs and Gray (1998) have derived a sample size formula for cost-effectiveness analysis based on a combination of the confidence intervals around

the costs and effects(89). The power calculation is dependent on some knowledge of the distribution, dispersion and variability of the data(86, 90). Cost or resource use data from previous studies or pilot studies can be used to estimate the sample size required(91). However, pilot studies are somewhat limited in terms of follow-up and the results tend not to be as variable as those reported in the final studies. Gray *et al.* (1997) found that the sample size required to detect a meaningful difference in cost was much larger than the sample size needed to detect a meaningful difference in clinical effect, and that in many published evaluations of community care, the trials were under powered to detect these cost differences(92). One reason why sample size calculations for economic data are rarely performed is that data on likely cost difference, distribution and variability is difficult to predict ex ante. Another related problem has been the lack of reporting of the variance and distribution of cost data. Briggs and Gray (1999) reported that out of a search of 492 cost-effectiveness and –utility studies only 53 were based on patient-specific cost data, and out of these only 25 studies reported any measure of variance(93).

Data collection centres

The resource use and unit cost data can be either collected from a single centre (e.g. hospital, GP practice, finance department) or a number of centres. The multi-centre approach adds to the generalisability of the study. It has been argued however, that where detailed resource use data collection has taken place, calculations of unit costs for each centre may not be necessary(94), moreover the use of centre-specific unit cost data may well mask the variations in resource-use. However, it might be illuminating to see whether and how much unit costs vary from centre to centre. Drummond *et al.* (1992) argued that centre-specific unit cost

data should be used in cases where unit costs are a function of resource use at individual centres(95). Empirical research into the decision of whether to collect both centre-specific resource use and unit cost data has been undertaken by Raikou and colleagues (2000). They show that the different methods result in statistically different estimates of average treatment costs, however they give no indication as to what is the correct method(96).

Choice of data collection tool

The choice of data collection tool is dependent on whether resource use information is being collected retrospectively or prospectively and the type of resource use information being obtained. Although any of the tools described below can be used alongside retrospective or prospective study designs, response rate, completeness and recall of data may be an issue. One has to trade-off collecting resource use information when the event occurs, and perhaps overloading the researcher and patient with questionnaires/diaries to fill in, with collecting resource use information after the event, and perhaps reducing the response rate, completeness and recall of events.

Interviews, questionnaires and diaries

Interviews, questionnaires and patient diaries are three ways of eliciting patient-specific resource use information directly from the patients. Interviews can be carried out on a face-to-face basis or over the telephone(97, 98). Questionnaires can be administered by post or handed out at the time of hospital or GP visit. They can be designed specifically to fit the study criteria, as with two studies by Sculpher and colleagues (1996) who used postal questionnaires to assess the resource use of women with treatment for menorrhagia(99, 100), alternatively, they

can be a standardised instrument, for example the CSRI (Client Service Receipt Instrument) designed to collect retrospective information on health and social service resource use(57), or the resource utilisation survey (RUS) developed by Copley-Merriman and colleagues for prospective use alongside trials(101). Diaries can be given to patients to record all resource utilisation. Diaries recorded the resource use incurred by parents of very low birth weight infants(102), the resource use related to elective total hip arthroplasty(103), low back pain(104) and cochlear implants(105). Case record forms (CRFs) are a type of questionnaire used in clinical trials to collect trial data. Medical personnel and/or the patients are asked to complete them. For the purpose of economic evaluations alongside clinical trials CRFs may be adapted to capture resource utilisation(106-108).

Questionnaires completed at the time of the patient's appointment is a cheap method of gaining resource use information, it also results in high response rates, compared with other techniques. Postal questionnaires are also a cheap method compared with interviews, but suffer from poor response rates. Both questionnaires and interviews suffer from recall bias if administered retrospectively, whereas patient diaries aim to overcome this bias by allowing all resource use to be noted down at the time of utilisation. Problems may arise if diaries are used over a long period of time; patient motivation for filling in the diaries is likely to decline over time, leading to the potential for missing data. Related to this aspect is the timing and frequency of the collection of resource use information. This is discussed in a separate section below.

Questionnaires can also be used to assess non-patient specific resource use information. They have been used to collect relevant information on equipment, instrumentation, consumables and staff (109).

Medical notes

All of the above examples of collecting patient specific data can be time consuming for the patient, especially if the disease being looked at is a chronic illness which incurs costs over a prolonged period of time, or involves phases of acute illness. It might also be the case that the study being conducted is of a retrospective nature and the sample of patients being analysed have already died. Thus medical notes, GP records and lab records may well prove to be a better (or only) source of data. For example Richards and colleagues (1993) used the medical notes of 50 patients diagnosed with advanced breast cancer to estimate the related costs(110) and Whynes *et al*, (1993) used the medical notes of colorectal cancer patients in order to cost their hospital treatment(111). However, medical records suffer their own limitations; records might be missing, stored elsewhere and difficult to access or destroyed (32), and when traceable they may be incomplete. More recently, the issue of obtaining patients' consent to access their medical notes has arisen(112). Accessing and abstracting data from medical notes can also be an extremely costly and time-consuming operation.

Databases

Databases provide an inexpensive and less time-consuming alternative for estimation of resource use but this may be at the expense of accuracy. There are two types of databases, administrative databases such as insurance claims or clinic/hospital databases that offer the opportunity to access patient-specific data and existing databases (e.g. cancer registry database) may be used to derive non-patient-specific data. Examples of use of these types of databases include studies by Lave et al, (1994) who discuss the strengths and weaknesses of Medicare databases for estimating costs(113) and Clermont and colleagues (1998) who

explored the feasibility of generating resource use data for ICU based on the Therapeutic Intervention Scoring System (TISS) from a database of hospital electronic billing data(114). Penberthy *et al,* (1999) used a combination of databases; they linked tumor registry data with Medicare administrative claims to determine the costs of care for breast, colorectal, lung and prostate cancers during the initial year subsequent to diagnosis(115). Databases, although advantageous in terms of large sample sizes, are limited in terms of missing data. In most cases they have originally been designed for another purpose and may not contain all the relevant data. In some cases misclassification of data can occur, for example, diagnosis, treatments undertaken etc. Another problem with databases is that some form of data abstraction has to be undertaken, this requires interpretation of the data by the coder, who requires training for that purpose.

Expert opinion

Information on resource use need not be patient specific, although this is argued to be the favoured technique. Estimates of resource use are sometimes obtained from a number of experts in the particular field of interest or Delphi panel. Expert panels are advantageous in terms of expense and time, as they offer a quick and inexpensive way of estimating resource use. However they may be limited in terms of accuracy, and can only provide deterministic data, which limits its use in the statistical analysis of costs and cost-effectiveness. A US study used clinician interviews using a Delphi technique validated by patient medical notes to ascertain the medical resource utilization when exploring the cost-effectiveness of paclitaxel (Taxol) + cisplatin compared to teniposide + cisplatin in advanced non-small cell lung cancer(116).

Observation

Observational techniques such as time and motion studies also provide non-patient specific (deterministic) data. This method of data collection offers a way of measuring staff workload, casemix, patient time spent, resource-use etc. and is therefore very useful when estimating unit costs in a micro costing study. Walker and colleagues (1991) used this observational technique when estimating the resource use and costs involved in various diagnostic procedures for colorectal cancer(117).

Piloting

Once decisions have been made about the sample size and sampling frame required, what data is required, where the data collection is to be carried out and what format this will take, the data collection methods need to be piloted. This represents an important step in the design of the study. It allows for the training of the data collectors and assessment of the acceptability and accuracy of the data collection tool chosen.

2.5 Analysis of Cost Data

2.5.1 Estimating total cost

Once the resource use and unit cost data have been collected the observed counts of separate categories of resources can be weighted by unit cost information and summed to provide an estimate of per patient total cost. The costs for each cost-generating event can be summed across the total time period of the study to provide total cost per patient. If the cost data is presented as average cost of detection or average lifetime cost or average cost by stage at diagnosis or average cost per

intervention it makes cost comparisons more understandable. This average total cost estimate is calculated by dividing the total cost by the relevant number of patients. These costs may be presented as life-time costs, annual costs, monthly costs, weekly costs or daily costs. The time period for which the costs are calculated depends on the time frame of the study or the duration of the trial. Cumulative costs can also be calculated for the given period of follow up. However, before these costs can be estimated, certain procedures need to be undertaken.

2.5.2 Adjusting costs for a base year

Costs are usually measured in the base year, for example, the year of disease diagnosis or the year of initial treatment. Therefore, if the unit costs being used relate to another price year they need to be adjusted for the effects of inflation using the Hospital and Community Health Services Pay and Price Index (HCHS pay and price index)(118).

2.5.3 Discounting

Discounting of costs is also required for converting future costs into present values thus allowing for differential timing of costs. The discount rate or factor used to convert a future stream of monetary amounts into its present value, accounts for time preference and opportunity cost. For example if an individual is indifferent between £1 today and £1.10 in a year's time, the implied annual rate of time preference is 10%. This is equivalent to using a discount rate of 0.1. Discounting is achieved by attaching smaller weights to future events. These weights are equal to $(1 + r)^{-t}$, where r = the discount rate and t is the year in which the event occurs. The question is what this rate of discount should be.

If there were perfect markets, the private and public rates of return on investments, and the individual and social rates of time preference would all be equal, and a single discount rate would exist. However markets are imperfect, therefore the discount rate can be equivalent to either the social rate of time preference, or the social opportunity cost. Both have inherent problems. Hence Drummond and colleagues (1987:52) suggest a criteria for selecting a *'central r'*(25)

1. Be consistent with economic theory (2% to 10%).
2. Include any government recommended rates (5%, 6%, 10%).
3. Include rates that have been used in other published studies to which you might wish to compare results.
4. Be consistent with 'current practice' (for example, 5 % has been used recently in papers published in the *New England Journal of Medicine*).

In practice different rates have been applied, but are generally between 3% and 6% (119-124)

2.6 Analysis and reporting resource use data

Ideally resource-use and cost information should be reported separately(125). There are a number of ways for analysing and reporting utilisation data. One can present the percentage of patients with contacts, for example 45% of the patients received a chest x-ray, however for some patients there may be several contacts or provision of the same procedure so this may ignore valuable information. Another method is to present resource utilisation measured as counts or frequencies of whether a service is provided to a patient, for example the number of x-rays. Finally, both methods can be used, for example 45% of the patients received an x-ray with a mean utilisation rate

of 3 x-rays per patient. Use of count data allows the distribution of counts to be compared.

2.7 Reporting cost data

The reporting of cost data is dependent on its method of collection. If non-patient-specific (deterministic) data have been collected costs are usually presented in terms of total cost and a point estimate of the mean cost. However if patient-specific data have been collected cost data should be reported in the form of total cost and average cost with some indication of the variance (for example standard deviation and 95% confidence intervals) and distribution of the costs. Estimation of the mean (average) cost is important for decision makers who require this information to assess the total budget required to provide a particular treatment or intervention. An estimate of this total budget (cost) is estimated by multiplying the arithmetic mean (average) cost of providing the intervention by the total number of patients requiring the intervention. Another important area in the analysis of health care costs is the comparison of the cost of different interventions. It is natural to explore whether the average per patient cost of one specified group differs from the average per patient cost of another group, for example whether costs of treatment differ between early stage and late stage breast cancer patients. Statistical tests such as t tests and one-way analysis of variance (ANOVA) are used to explore significant cost differences. It is impossible to determine this difference solely on point estimates of the mean difference, information on the variance of the cost data and its distribution is also required. A study by Briggs and Gray (1999) found that out of a total of 492 cost-effectiveness and cost-utility studies (published up to

1996), only 11% (53) were being conducted on a patient-specific basis, and out of these only 25 studies presented any information on cost variance(93).

2.7.1 Distribution and functional form of cost data

A problem encountered when analysing cost data is its distribution. This problem arises when statistical analysis of the cost data is required. In most cost data sets there exist a relatively small number of high cost patients that result in a positively skewed distribution. The implication of this skewed data is that the ability to detect significant differences between different groups is reduced; parametric tests are based on the distribution of data being normal. Therefore, according to standard statistical textbooks, unless the data are transformed these parametric tests should not be used and be replaced by non-parametric tests. However, it has been argued that as the sample size increases, parametric tests may be useful as the distribution is likely to reach normality(126).

There are inherent problems with using the three textbook methods of overcoming the problem of skewed data, use of the median, transformation and the use of non-parametric tests, when analysing cost data.

The median rather than the mean is sometimes used in the presence of skewed data. However, it is inappropriate to use this measure when dealing with statistical analysis of cost data. As health economists, we are interested in average and total cost estimates. The use of the median gives us neither estimate, when data is positively skewed the median is lower than the mean estimate, thus when this median is multiplied by total number of patients treated, the estimated result will differ from the true total cost for that group. Furthermore, estimating the measures of variance around the median can prove difficult.

Transformation, by taking the logarithm, natural log, square root, reciprocal or some other function, is an alternative method for handling skewed data. Briggs and Gray (1998) have shown that back-transformation of the log transformed costs can be made. They argue, however, that interpretation remains problematic due to the inability to back-transform to the original scale(19). In multivariate analysis of cost data this can be overcome by re-transforming using the process (known as the smearing estimator) outlined by a US statistician(127). However, the problem still remains that any form of re-transformation results in the analysis of geometric rather than arithmetic means. Geometric means are not appropriate summary statistics for economic analyses (as with the case of median measures). Two UK statisticians working with cost data(128), in response to the paper by Briggs and Gray (1998), have argued against the analysis of any form of transformed cost data, stating that:

"Analyses of costs should be based on untransformed data; any 'increased power' obtained by transforming the data is illusory as it is at the expense of addressing the wrong question" (128:255).

Non-parametric tests such as the Mann Whitney U test and the Wilcoxon sum rank test are used in situations where the assumptions required for parametric analysis of data are violated. However, these non-parametric tests address differences in the ranks of the raw data and report the medians (already shown above to be inappropriate). Coyle and Drummond (1996) have argued that since the objective of most statistical analysis of cost data is to compare means, non-parametric data based on medians may not be appropriate(94). Briggs and Gray (1998) have gone further, and argued that non-parametric tests do not address

inferences around arithmetic means, rather they compare the whole distribution of costs between groups.

Zhou and colleagues (1997) provide an alternative method of analysis for skewed cost data. They propose a Z-score method designed to adjust for skewness and compare means of log-normally distributed cost data(17).

One non-parametric method that has been proposed as an alternative method for the analysis of skewed cost data is bootstrapping(19, 129). Bootstrapping makes no assumptions about the distribution of the data, instead it employs the original data in a re-sampling exercise to empirically estimate the entire sampling distribution for the statistic of interest (in the case of cost the mean cost estimate). With bootstrapping the observed sample is treated as an empirical distribution and from this a random sample is taken from that distribution and the statistic of interest is calculated. This procedure is then repeated i.e. a re-sampling procedure is conducted. Random values are selected from the original sample (size n) with replacement[2.1] to yield a bootstrap sample of size n and the statistic of interest is calculated. A bootstrap sample may include the costs for some patients more than once, while excluding the costs for other patients. The process is repeated many times (by convention at least 1000 times). This gives a vector of bootstrap estimates of the statistic of interest, which is an empirical estimate of the sampling distribution of the statistic of interest.

[2.1] replacement means once a random value has been used for the bootstrap resample it is put back into the original sample so the same value can appear more than once in a bootstrap sample.

Because we are sampling with replacement, there will be variation between the samples. (N.B. sampling without replacement would simply yield the original sample and there would be no variation).

Although, limited work has been done on the appropriate way to handle the analysis of cost data given its skewed distribution (16-22, 92), no consensus has been reached as to the appropriate method. This issue of distribution of cost data is explored in more depth in Chapter 7, where I also look at issues of functional form and cost prediction.

2.7.2 Uncertainty of results

Once the cost analysis has been performed, it is important to recognise that the results are subject to uncertainties in the baseline parameters used. Uncertainty may arise from a number of sources; data inputs e.g. resource use data, unit cost data, methods used e.g. the discount rate, and assumptions made e.g. if the results are based on modelling or have been extrapolated. The certainty/uncertainty of the results needs to be quantified so that the researcher and subsequent users of the results know how much confidence to place on the results. There are two ways for analysing uncertainty relating to cost data, statistical analysis and sensitivity analysis.

Statistical analysis

The increased collection of patient-specific cost data has meant the ability to test for uncertainty using statistical tests to detect differences in mean costs and the presentation of measures of variability such as standard deviation and standard error. The methodology and its associated problems have already been discussed in section 2.6.1.

Sensitivity analysis

In practice, many economic evaluations do not use patient specific data, instead using data from a number of sources (literature reviews, clinical judgment), where statistical methods cannot be used. Even in studies where statistical analysis has been performed, an examination of the extent of uncertainty in certain point estimates (e.g. discount rate or unit cost data) should be undertaken. This is done by a process known as sensitivity analysis and involves the systematic investigation of how changes in the uncertain parameters affect the overall results(130).

Sensitivity analysis tends to be a subjective process, with the investigator deciding on which parameters may have an effect on the final results and selecting the level of variation required. The ranges across which to vary parameters is usually given as the highest and lowest ranges possible, or plus and minus 1 or 2 standard deviations, or use of 95% confidence intervals. The ranges and the amount of change incurred in baseline results should be specified. Briggs *et al.* (1994) have specified four types of sensitivity analysis, simple, threshold, analysis of extremes and probabilistic sensitivity analysis. Simple sensitivity analysis can be univariate or multivariate. Simple univariate sensitivity analysis requires one parameter to be changed to see what impact this has on the final result. However, it has been argued to be an incomplete estimate of the uncertainty as it takes no account of the interaction effects brought about by simultaneously changing several parameters. This is the case of a simple multivariate sensitivity analysis.

Threshold analysis identifies the critical value of the parameters above or below which the results of the study will change. Sensitivity analysis can also be carried out using the analysis of extremes approach, whereby a base case analysis is generated and then a further analyses is performed looking at extreme estimates.

Probabilistic sensitivity analysis uses Monte-Carlo analysis to simulate the distribution of the data. The issues surrounding handling uncertainty in economic evaluations have recently been reviewed by Briggs and Gray, (1999). They discuss in detail the different types of uncertainty arising in economic evaluations and the distinct forms of sensitivity analyses that can be undertaken to account for this uncertainty(93).

2.8 Other issues pertaining to the analysis of cost data

2.8.1 Missing and censored data

Missing data is an inherent problem common to the majority of economic studies. Data can be missing for a number of reasons; patients may not return or complete data collection instruments, or it may arise due to loss to follow up where a patient drops out of a trial or information in the medical notes is no longer recorded. Missing data may therefore have implications for the analysis of the cost data and requires some decision to be made as to how to handle it. Non random approaches to handling missing data exist, one approach is to ignore it (available case analysis), another is to delete the cases where any data is missing and base the analysis on the cases with complete data (complete case analysis). An alternative method is to replace the missing data with imputed values. The imputed values may be the mean values of the non-missing data (mean imputation). Replacement by imputation may in fact be biased and reduce the true variability of the data(94). Conditional mean imputation can get around this problem of reduced variability, by conditioning the mean values to be imputed on certain observed characteristics such as age, gender, stage of disease. Moreover, data (especially trial data) are

seldom missing at random, and Crawford *et al.* (1995) suggest that regression imputation provides an easily implemented method of adjustment for non-random non-response(131). A review of these methods can be found elsewhere(132).

Where data are missing due to loss to follow up/attrition i.e. right censored, several approaches have been suggested to account for this when estimating the mean total cost. One approach is to assign zero costs for the censored period, Rutten van Molken *et al.* (1994) have argued that this may underestimate the costs and suggest carrying forward the mean costs of all observations for patients with limited follow up(35). They argue that this is appropriate because the high level of resource-use at time of censoring would have been sustained or may have even increased. Fenn *et al.* (1996) have adopted techniques of survival analysis to extrapolate treatment costs beyond the end of the trial(14). Lin *et al.* (1997) (15) have suggested partitioning the survival curve into intervals and estimating the costs for each interval. This issue of missing data is discussed in more detail in chapter 9 with examples using the Trent cancer cost data.

2.9 Discussion

This chapter has documented the methods, recommendations and issues related to costing. From this review it is noticeable that some of the methods presented are current accepted conventions[2.2] and undertaken by all health economists, while other methods are debatable with no consensus on the correct technique to be used,

[2.2] While economists by their nature are always likely to disagree, there are methods and issues where general consensus has been reached.

and finally, there are new emerging methods and techniques that require more empirical research.

1. **Areas of current accepted conventions in costing:**

- Measurement and valuation of direct health care costs.
- Measurement and valuation of direct non-health care costs.
- Measurement of informal care.
- Use of pilot questionnaires.
- Choice of time horizon; this should cover the period in which all the main cost-generating events are incurred.
- Requirements for reporting the results; average cost, with an indication of the variance of the cost, an estimate of the total cost of implementing the intervention. Where comparisons are made a statement of the statistical test used and results of the test.
- Statement of any adjustments used in base year prices and how they were adjusted.
- Statement of the currency in which the costs are reported.
- Use of discounting.
- Use of sensitivity analysis to assess areas of uncertainty in cost results.

2. **Current unresolved/debatable issues**

- The choice of perspective. Most of the existing economic evaluation guidelines argue that a societal perspective should be used for all analyses, while others have argued that the choice should be dependent on the target audience or the funding body who commissioned the study. For example

the National Institute for Clinical Excellence (NICE) has taken the perspective of the NHS or Social Services for its evaluations.

- The choice of data collection tool; in some respects the choice is determined by the type of study being conducted, whether it is prospective and alongside a trial or prospective and naturalistic or retrospective. However more research is required on the validity and reliability of the current data collection tools used, and it would be useful to be able to have more direct comparisons between instruments.
- The valuation of informal care costs, whether the opportunity cost or replacement cost approach should be used.
- Whether productivity costs should be included in the total cost estimate. This debate is dependent on the reason for costing, if it is to estimate the total burden of a particular disease, it is useful to include the cost due to lost productivity arising from the morbidity or mortality caused by the disease. However, if the costing process is being undertaken as part of an economic evaluation, whether to include indirect costs as part of the cost estimate (numerator of the CER) or the benefit estimate (denominator of the CER) is undecided.
- If it is decided that productivity costs should be included in the total cost estimate, there remains a debate as how to measure and value these costs. In general, lost productivity is valued using the human capital approach, whereby an average earnings figure is attached to the amount of productive time lost due to the disease or illness. However, it is the measurement of this time that has been the undetermined issue.

- The inclusion or exclusion of future related and unrelated costs. Although an old topic of debate, it has been resurrected recently by Meltzer (1997) and Garber and Phelps (1997) (consensus on this issue is yet to be reached).
- What rate of discount should be used? This has been widely debated, and varies according to which country the analysis was undertaken. However, the UK tends to use the rate of 6% for costs reflecting current advice from the Treasury to the whole of the public sector.
- Type of sensitivity analysis; the type of sensitivity analysis undertaken by the researcher is largely dependent on the data collected, of all the types it has been argued that probabilistic sensitivity analysis provides the most useful information for the decision maker.

3. Areas of emerging methodological techniques, where further empirical research is required.

- Choice of data collection centres. As increasing numbers of economic evaluations are conducted alongside multi-centre clinical trials, a debate has emerged as to what is the appropriate method for collecting resource use and unit cost data. The question is whether to collect centre specific resource use and centre-specific unit cost data or to use average unit cost data and attach this to centre specific resource use data. It is surprising to find that only one study has looked at this question empirically, and this is limited in that it uses simulated clinical trial data(96).
- Ways of controlling for skewed cost data. Over the past four years there has been an emergence of published research looking at how to analyse costs in the presence of positively skewed data. The choice is between

transforming the data so as to normalise the distribution, use non-parametric hypothesis tests such as the Mann-Witney, use bootstrapping, leave the data untransformed and undertake parametric hypothesis tests.

- Missing and censored data. In the past cost analysis has been performed with no account taken of any data that may have been missing. It is only in the past five years that health economists have been alerted to the problems connected with missing or censored data. Further research is required to understand the changes in results when using the different methods proposed to take account of missing or censored resource-use/cost data.

This chapter has introduced the concept of economic costing as used by health economists. The purpose was to review the literature on methods, issues and guidelines related to costing, with the aim of informing the methods and techniques to be used in this thesis[2.3]. In reviewing the literature four questions were addressed, 1) What are costs? 2) Why are we interested in costs? 3) How are costs estimated? and 4) How should costs be analysed? This chapter therefore presents a descriptive outline of how the process of costing ought to be undertaken and how the issues related to costing be handled. The process of costing is a complex task, and rarely is it possible for the analyst to incorporate all relevant costs or to estimate the true opportunity cost of the resources used. In practice a trade-off must be made between the time and expense in collecting resource use information

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[2.3] It should be noted that this review was initially undertaken in October-December 1994, and therefore a very limited set of the literature used in this chapter (published pre-1995) was used to inform the initial methods for this thesis.

and estimating costs and the integrity of the study. All studies are constrained by time and finance. The next chapter (chapter 3) explores the issue of the transferability of these costing guidelines into practice.

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Appendix 2.1 Capital Costing

Capital costs, for example, land, buildings and equipment are incurred at a single point in time, usually at the start of a programme. However, they are used over time and despite the initial outlay the opportunity costs are spread over time. Thus capital costs consist of two elements; the opportunity cost i.e. the foregone opportunity by investing the sum of money in that particular asset, and the depreciation factor (over time the value of the asset depreciates[A2.1]).
There are two ways of dealing with capital costs:
If the market rate exists for the rental of buildings or the lease of equipment, these can be used to estimate the capital cost. The most widely used method advocated by Richardson and Gafni (1983) and Drummond *et al.* (1994) (25, 133) incorporates both the depreciation and opportunity cost aspects. This involves annuitizing the initial capital outlay over the useful life-span of the asset, i.e. estimating the equivalent annual cost. This still requires knowledge of the initial value of the resources and the appropriate rate of interest.
Below is the relevant equation for annuitizing an asset over its expected useful life-span. If the initial capital outlay is C_i, one needs to find the annual sum A, which over a period of Y years (life of asset), at an interest rate R, will be equivalent to C_i:

$$A = \frac{C_i}{P_i}\left[\sum_{n=1}^{y}(1+R)^n\right]^{-1}$$

Where:

C_i = Capital spent in year i
P_i = Price index for that year relative to the current year
R = Constant discount rate
Y = Expected years of use of the item

This equation may have to be altered for the age of the equipment as there is variation between new and old equipment. The method for the annuitization of new equipment is straight forward, the value is taken to be the initial capital outlay annuitized over its useful life span. However with old equipment, one can either use the replacement cost and discount over its full life, or use the current market value of the old machine and its remaining life. The former is considered to be more generalizable and therefore more reliable (25).

A2.1 The cost of land is equivalent only to its opportunity cost, there is no depreciation factor.

Chapter 3

Estimating Costs In Practice

3.1 Introduction

In the review of methods, issues and guidelines for cost estimation in the previous chapter, there was a mixture of literature on guidelines and methods for costing for the purpose of cost of illness studies and economic evaluations. Also included in the review were 'one-off' guidelines for specialised areas of cost estimation and analysis, for example, sensitivity analysis(1, 2), how to deal with skewed cost data in analysis(3, 4), and censored cost data(5, 6) etc. These published guidelines for cost estimation (the majority of which were found in texts or published papers on guidelines to economic evaluations) provide advice on how in principle cost estimation should be carried out. Economic principles (outlined in chapter 1) coupled with the requirement for transparency and transferability have shaped these guidelines. The aim of this chapter is to clarify three questions:

1. to gauge the number and nature of studies that have estimated costs with respect to the disease cancer;
2. to examine how the methods and principles of cost estimation explored in chapter 2, transfer into practice;
3. to highlight the methods used and problems that may arise in the estimation and analysis of costs of cancer.

In order to respond to these questions a literature review of costing and cost estimation with specific reference to the disease, cancer, was performed. The literature search was conducted using electronic bibliographic packages to identify the source of publications. It is however, unlikely that this search is inclusive[3.1]. In the subsequent chapters on breast, cervical and lung cancer costs, further studies (published and unpublished) have been identified by utilising sources other than the bibliographic packages. For example, use of sources of reference in published studies, colleagues' advice and information on published and unpublished studies.

3.2 Methods

The first aim of the review was to identify any research on the subject area of cost or economics of cancer or cancer care. After having defined the objectives of the review, the next step was to identify the eligible studies. Literature on the costs and cost-effectiveness of cancer and cancer care were detected using electronic database searches. These included:

- Embase (1980 to present)
- Sci search via BIDS (1981 to present)
- Soc Sci search via BIDS (1981 to present)
- Medline (1966 to present)
- NHS Economic Evaluation Database (compiled by the Centre for Reviews and Dissemination at York University - whole database)

All the above database searches were conducted during August 1998. However some of the publications during the first eight months of 1998 may have been excluded due to time lags between publication and citation in the databases.

[3.1] It should be noted that it was not the purpose of this chapter to conduct a comprehensive search on all the published and unpublished literature on the topic of cost of cancer.

Studies were included if they appeared to assess the direct and/or the indirect cost of cancer or cancer care. Review studies were included in this initial search. The exclusion criteria for this initial search were purposely kept to a minimum as I required a comprehensive list of published studies on cost and cancer. Exclusions were made if the studies were clearly not anything to do with costing or cancer. In some cases when reading the abstract it was difficult to determine whether a cost analysis had been conducted or whether they were simply reporting resource use. If only resource use was reported these studies were excluded from the review. The searches were also limited to 'English language' and 'human' studies. Understandably a number of studies that appeared to meet with the inclusion criteria during the initial review were subsequently excluded; titles and abstracts can be misleading. Thus, once all the literature that appeared to satisfy the inclusion criteria were gathered, and the papers read in more detail, further exclusions had to be made. Table 3.1 reports the results from the literature search.

From the original set of 595 papers which appeared to be of interest, a number of publications were found to be duplicates or triplicates (i.e. cited by more than one bibliographic package), or not appropriate for inclusion into the review because the paper gave no information on either cost or cancer or in some cases both subject terms. Therefore the number of papers eligible for the review was reduced to 383 (Appendices 3.1 and 3.2).

Table 3.1 Results from the Literature search

EMBASE:

'cancer' or 'neoplasms' = 29,288
limit to 'English' and 'Human' = 18,619
'cost' (include all terms) = 47,039
limit to 'English' and 'Human' = 25,444
combine = 223
of interest = 22

Sci Search BIDS:

search in the title, keywords/abstract field
'cancer and cost' = 2,672
of interest = 280

SocSci Search BIDS:

search in the title, keywords/abstract field
'cancer and cost' = 394
of interest = 86

Medline:

'cancer' (include all terms) = 95,713
limit to 'English' and 'Human' = 66,802
'cost': 'cost & cost analysis'
'direct service costs'
'drug costs'
'employer health costs'
'hospital costs' = 29,208
limit to 'English' and 'Human' = 18,532
'economics': 'medical' = 17,338
'hospital'
'nursing'
'pharmaceutical'
limit to 'English' and 'Human' = 5,919
'cost-benefit analysis' = 15,803
limit to 'English' and 'Human' = 12,290
'cost of illness' = 1,630
limit to 'English' and 'Human' = 1,449
combine
'cancer' and 'cost' = 325
'cancer' and 'economics' = 47
'cancer' and ' CBA' = 224
'cancer' and 'cost of illness' = 49
of interest = 92

NHS Economic Evaluation Database - CRD

'cancer' = 126
'cancer' + 'cost' = 123
of interest = 115

3.2.1 Categorization of study type:

Not all the studies in the review were reports of costs or economic research, although all had some element of cost in them. I therefore decided to categorize them according to study type:

1) Economic evaluation:

Cost-effectiveness analysis (CEA)

Cost-utility analysis (CUA)

Cost-benefit analysis (CBA)

Cost-minimisation analysis (CMA)

2) Other cost study, e.g. cost of illness or cost of disease/ process/ treatment.

3) Review studies of economic aspects of cancer care or economic evaluations of care.

4) Guidelines/description of methods used for cost estimation of cancer and cancer care.

5) Other - e.g. conference proceedings, editorials, letters.

Further exclusions to the 383 publications were made; review or guideline papers, letters, conference proceedings and editorials were excluded from any detailed analyses. The reason for these exclusions was that primary research studies were required for such a review of the practical elements of costing. The remaining 262 papers were classified according to disease/cancer site or treatment type, year of publication, country from which the study originates (see section 3.3).

As the main aim of this review was to ascertain whether the practical and applied costing adhered to the theory set out in the guidelines outlined in Chapter 2. A detailed review of a single paper took three hours on average. To attempt a detailed

examination of all papers that met with the inclusion criteria would have therefore taken a considerable amount of time. It was therefore felt to be impractical to review all 262 papers in detail. The number of papers for detailed review needed to be reduced. A 15% random sub-sample of the 262 papers that met with the inclusion criteria was selected for intensive detailed review of the costing methodology used.

The detailed review required a decision on a number of study criteria to which an assessment of adherence could be made. The choice of criteria was based on the methods, guidelines and issues discussed in Chapter 2. These criteria along with the background information required for the review are set out in Table 3.2.

Table 3.2 Background information and criteria for the review of published studies of costing and cancer.

- **Author**
- **Year**
- **Type of economic study:**
  - CCA
  - CBA
  - CMA
  - CEA
  - CUA
- **Type of health care strategy:**
  - treatment
  - prevention
  - diagnostic
- **Type of cancer**
- **Type of intervention**
- **Viewpoint/ perspective:**
  - patient
  - health service
  - society
- **Type of cost:**
  - direct health care
  - direct non-health care
  - informal
  - productivity
- **Study design: retrospective or prospective analysis**
- **Stochastic or deterministic analysis**
- **Time horizon**
- **Relevant costs included**
- **Data collection centre**
  -single centre or multi-centre
- **Sample size calculation**
- **Quantification of resource use:**
  - previous studies
  - medical records
  - RCT

- literature search
- clinical advice/ Delphi panels
- interviews/patient diaries
- observation

- **Valuation of cost estimation:**
  - cost of resources from estimation
  - unit costs of resources from finance
  - prices: billing data, tariffs
  - published studies
- **Costs and resource use information stated separately**
- **Price base:**
  - use of Hospital and Community Health Services pay and price index or RPI to change price base
- **Currency:**
  - use of exchange rate or Purchasing Power Parity to convert currencies
- **Discounting**
- **Analysis of cost data:**
  - statistical analysis and reporting of costs
- **Costs varied in sensitivity analysis:**
  - one way
  - multiway
  - probabilistic
  - analysis of extremes
  - threshold
- **Handling of missing data**

3.3 Results from the review

From the 383 studies identified in the electronic databases, 262 were eligible for further analysis (see Appendix 3.1). 121 of the papers were excluded for the following reasons; 17 were conference proceedings, 6 were editorials, 4 were guidelines to costing, 21 were letters, 64 were review articles, 2 were a mix of guidelines and reviews, 6 were found to have no English translation available and 1 could not be traced by inter-library loans (Appendix 3.2). The 262 left for further analysis, have been categorized according to; economic study type (Figure 3.1), country where the study was carried out (Figure 3.2), cancer site or specific therapy (Table 3.3), publication year (Figure 3.3) and author of study (Table 3.4).

Figure 3.1 Type of economic study

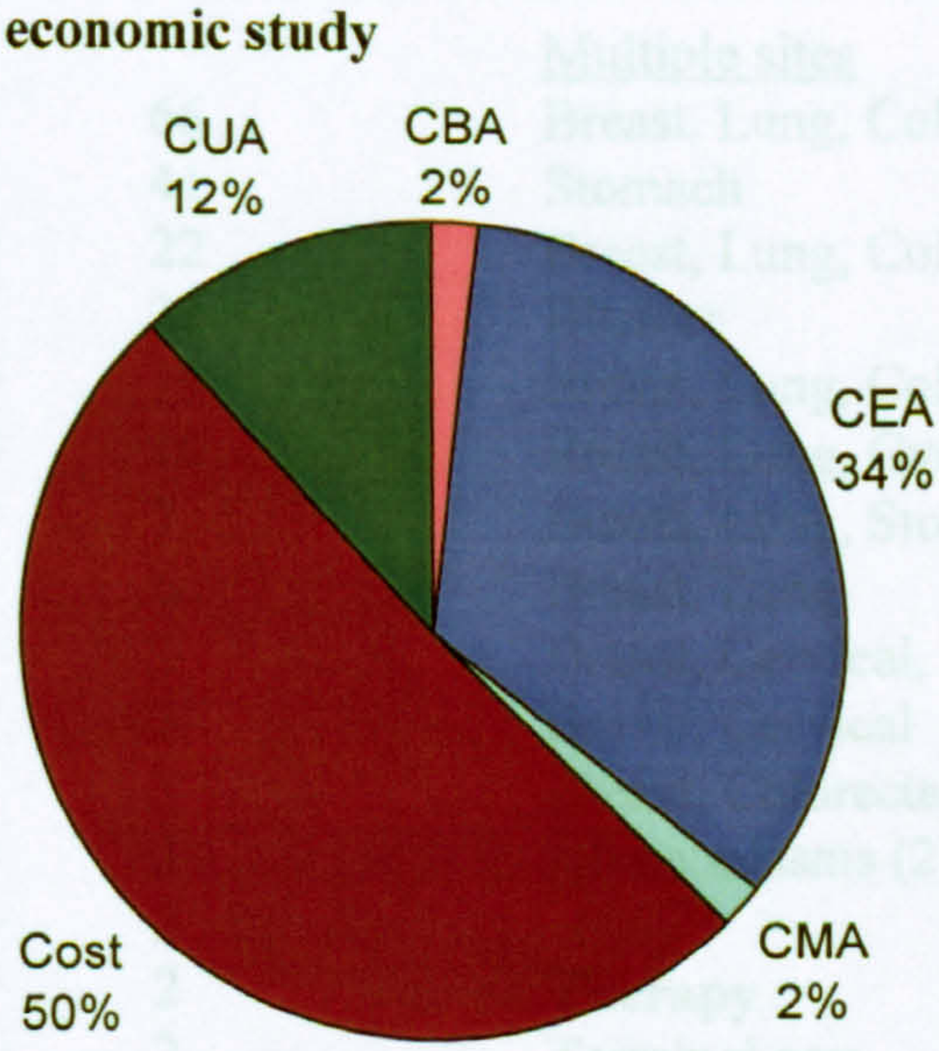


Figure 3.2 Country where study was undertaken

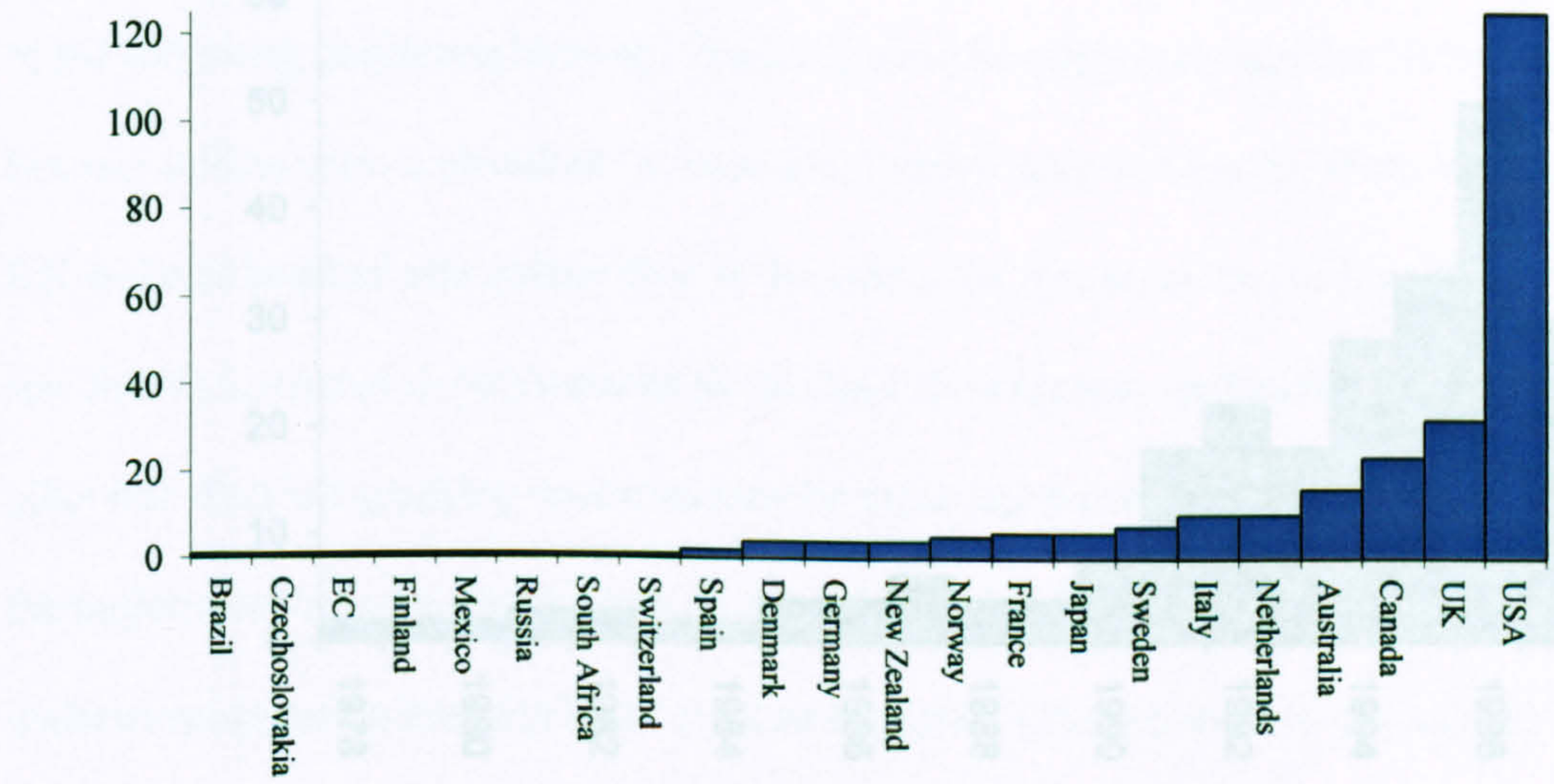


Table 3.3 Cancer site or specific therapy

Site		**Multiple sites**	11:
Breast	66	Breast, Lung, Colorectal, Prostate,	
Colorectal	41	Stomach	
Cervical	22	Breast, Lung, Colorectal, Prostate,	
Prostate	22	Bladder	
Lung	19	Breast, Lung, Colorectal	
Ovarian	10	Breast, Lung, Ovarian	
Cancer	7	Breast, Lung, Stomach, Uterus	
Stomach	6	Breast, Lung	
Testicular	3	Breast, Cervical, Colorectal	
Endometrial	3	Breast, Cervical	
Melanoma	3	Breast, Colorectal, Prostate	
Brain	2	All neoplasms (2)	
Childhood	2		
Hodgkins	2	**Therapy**	
Leukemia	2	Terminal care	11
Bladder	1	Chemotherapy	10
Head and neck	1	Radiotherapy	4
Non-Hodgkins	1	Anti-emetics	3
Oesophagus	1	Radiology	3
Oral	1	Pain	3
Pancreas	1		
Upper aerodigestive tract	1		

Figure 3.3 Year of publication

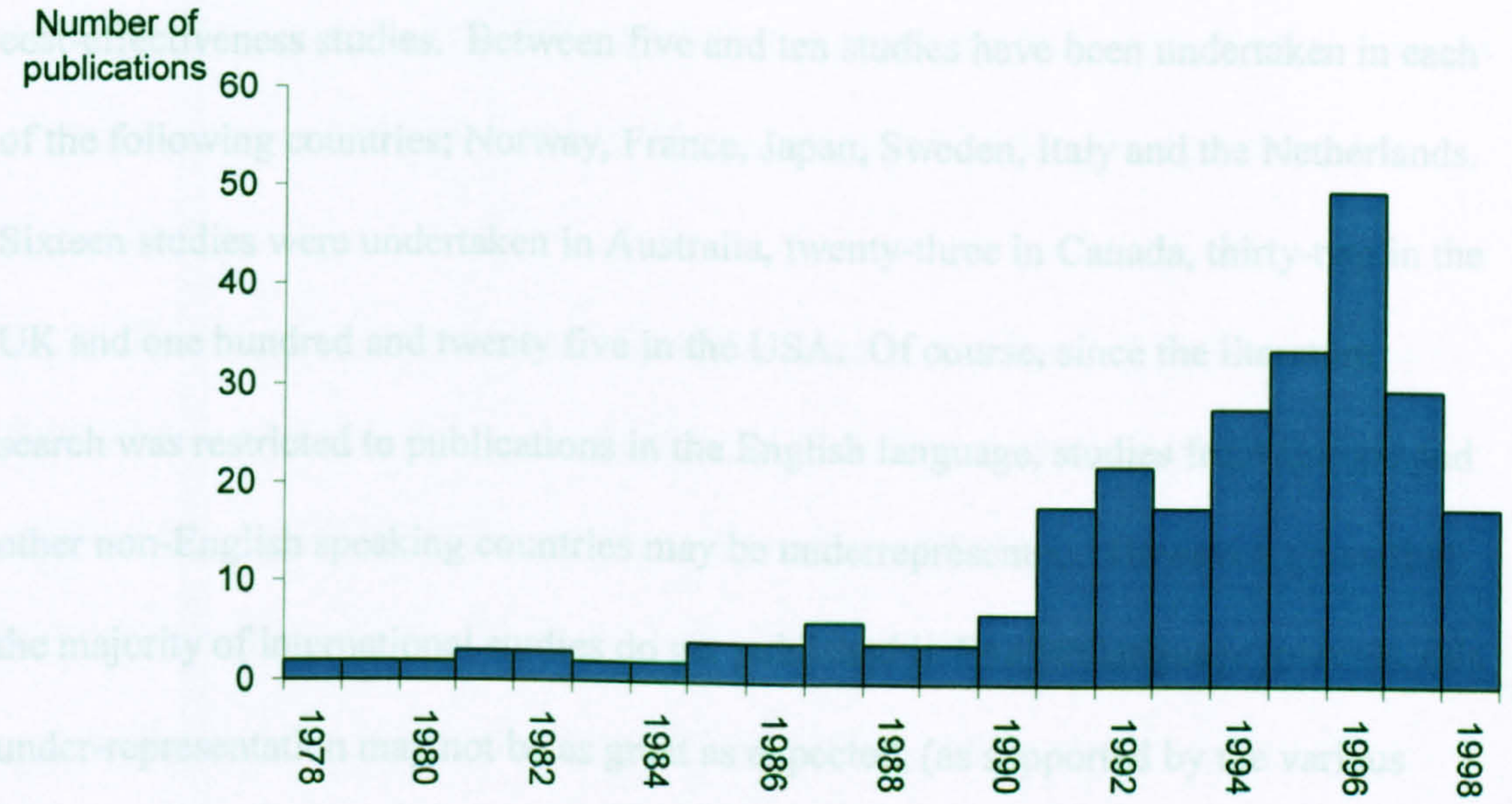


Table 3.4 Authors of publications concerned with 'cancer' and 'costing' where numbers of publications are >1

Hillner BE	13	van der Maas PJ	3
Smith T	11	Virgo KS	3
Whynes DK	8	Waugh N	3
Evans WK	7	Baker MS	2
Walker A	7	Bastin K	2
Koopmanschap MA	6	Bennett CL	2
Brown ML	4	Butler JRG	2
de Koning HJ	4	Goodwin PJ	2
Gyrd-Hansen D	4	Hall J	2
Messori A	4	Hodgson T	2
Norum J	4	Hutton J	2
Salkeld G	4	Jonsson B	2
van Ballegoijen M	4	Launois R	2
van Inveld BM	4	Leese B	2
Arveux P	3	Lieberman D	2
Carlsson P	3	Lokich JC	2
Fahs MC	3	Neilson A	2
Hurley SF	3	Simon MS	2
Lindfors KK	3	Tsuji I	2
Littrup PJ	3	Weeks J	2
Mandelblatt JS	3	Wodinsky HB	2
Rosenquist CJ	3		

Fifty per cent of the studies are categorised as cost studies, thirty-four per cent are cost-effectiveness studies. Between five and ten studies have been undertaken in each of the following countries; Norway, France, Japan, Sweden, Italy and the Netherlands. Sixteen studies were undertaken in Australia, twenty-three in Canada, thirty-two in the UK and one hundred and twenty five in the USA. Of course, since the literature search was restricted to publications in the English language, studies from Europe and other non-English speaking countries may be underrepresented. However, given that the majority of international studies do get published in English language journals, this under-representation may not be as great as expected, (as supported by the various countries included in the review (Figure 3.2)). The under-representation is more likely to be concentrated on specific countries such as studies from China and Russia.

Unsurprisingly, most of the studies reported in the literature examine the most common cancers. Sixty-five per cent of the 262 studies considered breast, cervical, prostate, lung or colorectal cancer. Breast cancer alone accounted for twenty five per cent of all the studies in the review. The majority of the studies (86%) on cost and cancer were published in the 1990's, with fifty published in 1996 alone. It must be remembered that the figures for 1998 are only for 8 months of the year as this literature search was carried out in August of that year, moreover there are time lags between publication and being entered into the electronic databases. Therefore the figure of 18 for 1998 is likely in reality to be much higher. The final categorisation of the 262 studies was by author of the paper. Fifty-eight per cent of the total number of studies were by first authors who had published more than 1 study out of the 262.

3.4 Detailed Review

A 15% random sample of the 262 papers that met with the inclusion criteria resulted in a detailed review of 40 publications. The papers in this review are documented in Appendix 3.3.

3.4.1 Background information of publications in the detailed review

Tables 3.5 and 3.6 give background information such as study type and year of publication. This information closely matches that of the 262 published papers found in the literature review (see Figures 3.1 and 3.3), with 50 per cent of the studies being cost studies and the majority being published in 1994-1997.

Table 3.5 Study type (detailed review)

Study type	Number	% of total
Cost	19	47.5
CEA	13	32.5
CUA	5	12.5
CMA	2	5
CBA	1	2.5

Table 3.6 Year of publication (detailed review)

Year of publication	Number	% of total
1979	1	2.5
1980	1	2.5
1983	1	2.5
1986	1	2.5
1987	2	5
1988	1	2.5
1989	1	2.5
1990	1	2.5
1991	2	5
1992	1	2.5
1993	4	10
1994	7	17.5
1995	5	12.5
1996	5	12.5
1997	5	12.5
1998	2	5

Type of health care strategy

Of the 40 studies, 29 (73%) are categorized as treatment studies, while 8 (20%) are prevention studies and 3 (8%) investigate diagnostic procedures.

Type of intervention

Exploring the type of interventions looked at in the papers, screening contributed to 8 of the papers (20 %), as did chemotherapy. Other interventions included diagnostic procedures such as biopsy(7) or radiology(8), or the entire disease management of specific cancer sites(9-13).

Type of cancer

Costs were estimated in the studies for a range of cancer sites (Table 3.7). Breast cancer accounted for 5 papers (12.5 per cent of the total), while colorectal cancer made up 15 per cent of the total (6 papers), lung cancer accounted for 10 per cent of the total (4 papers), cervical cancer, prostate cancer and chemotherapy accounting for 3 papers each (7.5 per cent each).

Table 3.7 Cancer site or specific therapy (detailed review)

Cancer site	Number of papers	% of total
Colorectal	6	15
Breast	5	12.5
Lung	4	10
Cervical	3	7.5
Chemotherapy	3	7.5
Prostate	3	7.5
Cancer	2	5
Endometrial	2	5
Terminal	2	5
Other	10	25

The above, all represent background information to the papers reviewed. However the main purpose of the detailed part of the review was to look at the costing methodologies used.

3.4.2 Costing methods used in publications in the detailed review

Viewpoint/perspective of the study

The first area of interest in any costing study is what is the viewpoint or perspective of the study. Out of the 40 studies looked at, 31 were from the perspective of the health service, 6 were based on a societal perspective, and 2 from the USA were from the 'payors' perspective.

The type of perspective chosen governs the type of cost to be estimated. For all cases, the direct health care cost was ascertained (Table 3.8), four of these studies also estimated the direct non-health care costs, i.e. the patients' and families' travel costs or any other direct payments made by the patient or family as a result of receiving the medical care(12, 14-16). Three studies estimated the productivity costs related to the disease(10-12). Informal care costs were estimated by Lansky and colleagues (1979) when estimating the non-medical costs of childhood cancer (15).

Table 3.8 Type of cost

Type of cost	Number of studies	Percentage of studies
Direct health care costs	40	100%
Direct non-health care costs	4	10%
Informal care costs	1	3%
Productivity costs	3	8%

Prospective, Retrospective or Model

The studies differ in the type of design. The design is an important factor to consider as it impacts on how the resources are identified, measured and valued, and whether the information collected is stochastic or deterministic, and whether statistical analysis and/or sensitivity analysis of the cost data is undertaken.

Figure 3.4 Proportion of articles by study type

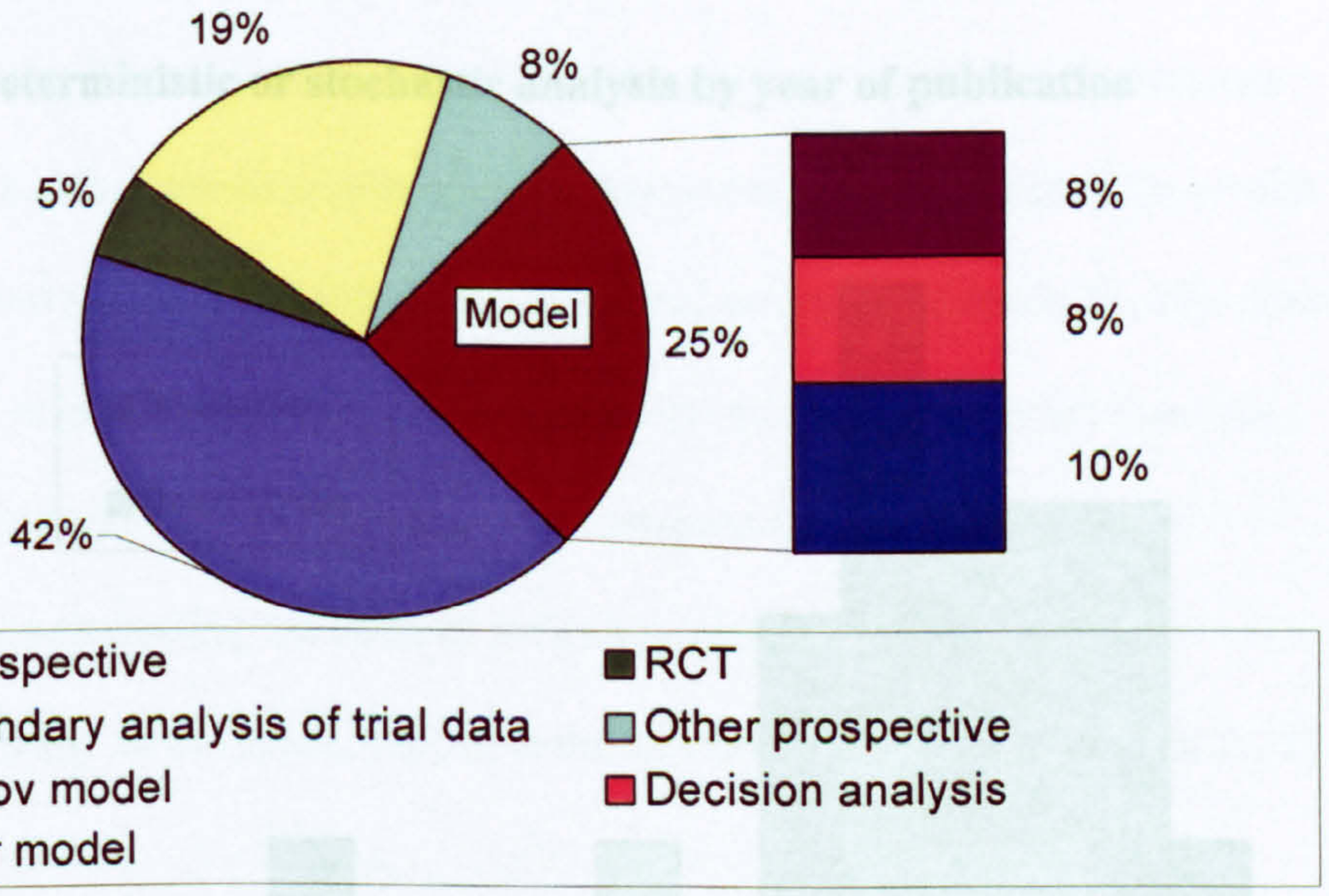


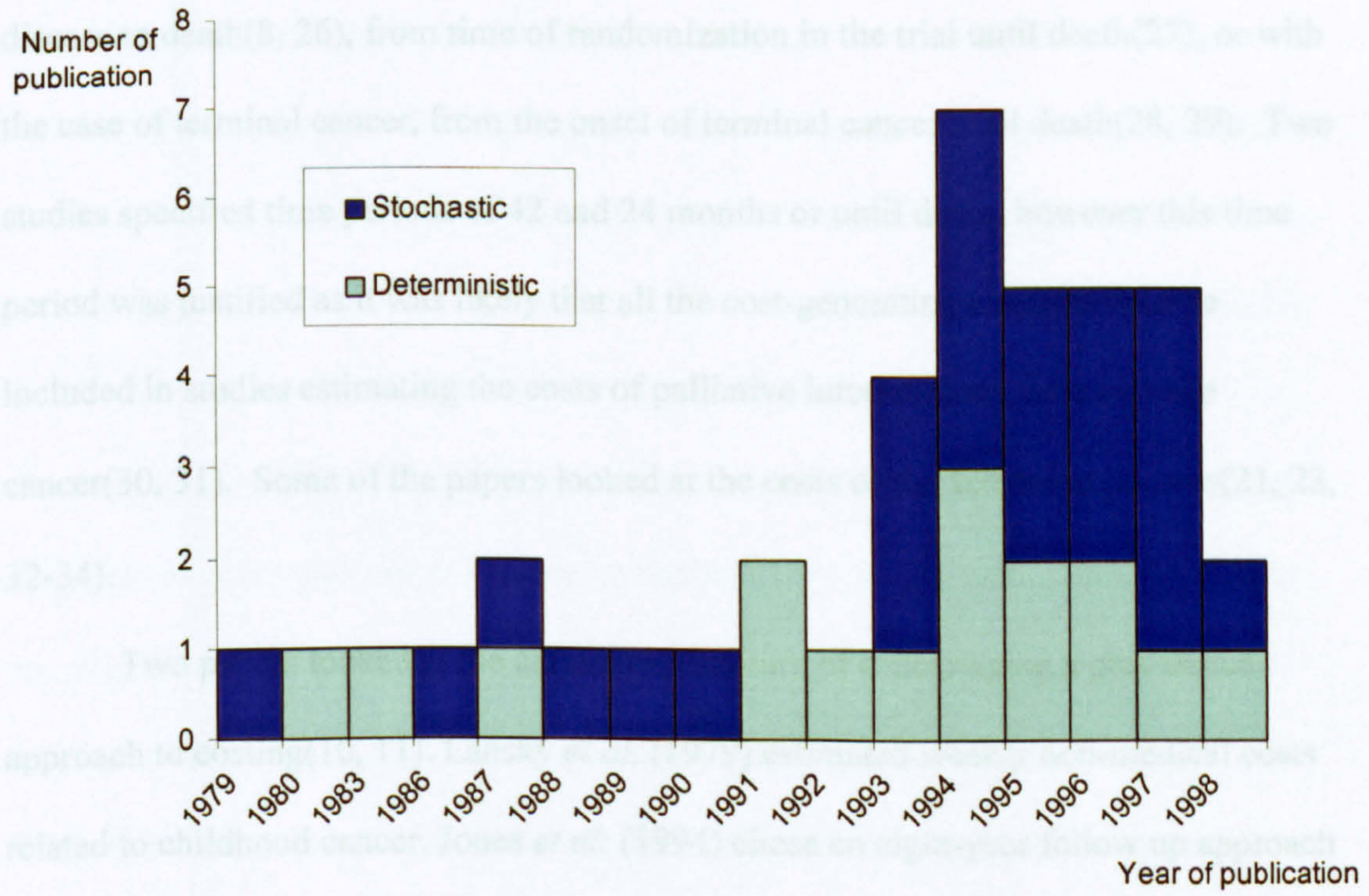
Figure 3.4 summarises the various designs used in the 40 published studies. Forty-three percent of the studies had been carried out on a retrospective basis, usually using a retrospective case series of patients. A secondary analysis of trial data had been conducted in 19% of the studies, and in 5% they were conducted prospectively alongside an RCT. Eight per cent of the studies had also been conducted prospectively, but not alongside a trial. Finally 25% of the studies used some form of modelling based approach. Fahs *et al.* (1992), Shimbo *et al.* (1991) and Smith *et al.*

(1993) all use Markov models. Others used decision-analytic models to estimate the cost-effectiveness of treatments(7, 17-19), or other forms of mathematical simulation(20-23).

Deterministic versus Stochastic analysis

Figure 3.5 displays the nature of the study in terms of patient-specific (stochastic) data or non-patient-specific (deterministic) data, by publication year. Whether patient-specific data collection and analysis has increased over time; no clear inference can be made from this review of 40 publications.

Figure 3.5 Deterministic or stochastic analysis by year of publication



Time horizon

Another important area in costing is the time period over which the costs/resource use is related. This time horizon can indicate whether all the relevant costs are included. In order to make the costing methodology transparent, published papers should state the time period used for costing. However, in this review, 10 of the papers gave no indication of the time period used. Twenty-three appeared to have adequate follow up time and included relevant costs for the cancer type. For example, 7 studies looked at the cost of the whole disease process(9, 13, 14, 18, 20, 24, 25). Others simply looked at the costs from the diagnosis of the event to death e.g. from diagnosis of advanced disease to death(8, 26), from time of randomization in the trial until death(27), or with the case of terminal cancer, from the onset of terminal cancer until death(28, 29). Two studies specified time periods of 42 and 24 months or until death, however this time period was justified as it was likely that all the cost-generating events would be included in studies estimating the costs of palliative interventions for end-stage cancer(30, 31). Some of the papers looked at the costs of the screening process(21, 23, 32-34).

Two papers looked at the annual expenditure of cancer using a prevalence approach to costing(10, 11). Lansky *et al.* (1979) estimated weekly non-medical costs related to childhood cancer. Jones *et al.* (1994) chose an eight-year follow up approach following brachytherapy for cervical cancer. Similarly the study conducted by Layfield *et al.* (1993) encompassed all the costs by following up the patients diagnosed with breast cancer for ten years.

Are the relevant costs included?

Seven papers appeared to have inadequate time periods, and hence did not reflect the true costs of the disease or intervention being looked at. Smith *et al.* (1997), when evaluating the treatment costs of Hodgkins and non-Hodgkins disease, considered the resource use and cost solely for the trial period. No statement was made in the paper as to the length of the trial period, however it was clear that no follow up time was costed.

Messori and colleagues, (1997), assessing the cost of treatment for melanoma used a follow up time of one year and then made the assumption that follow up costs after this period were the same for both trial arms.

"*After the first year, the follow-up costs for those two patient groups were assumed to be identical (e.g. number and length of hospitalizations, laboratory tests, expenditure for treating drug-related side-effects, costs of terminal illness etc.)*" (37:1374-1375).

Whynes *et al.* (1993) may well have missed out on important costs of recurrences and complications by restricting the time period to three years following diagnosis of colorectal cancer. However one must weigh up the feasibility of follow up. If carried out prospectively, this can be an expensive process, yet if carried out retrospectively, with cancer there can be a problem of accessing relevant data. Whynes and colleagues actually qualify their choice of three years by stating:

"*To assess the economic impact of the disease more fully, treatment costs for each patient were calculated over a 3-year period (or until death, if occurring within this period), starting from the date of diagnosis in each case. The choice of three years as a cut-off point was dictated by (i) the need to generate a sample of sufficiently large*

size to permit statistical inference, (ii) clinical findings, which suggest that the majority of complications and cancer recurrences are likely to occur within 1-2 years of the initial intervention." (38:965).

Jones and colleagues (1994), when comparing the cost of two types of brachytherapy for the treatment of cervical cancer, state that they have used an eight-year time horizon as this is the potential useful life of the caesium implant used in this type of therapy. However, they fail to include any of the costs incurred over the time period of the follow up and complications related to the therapy.

Ortega *et al.* (1997) based their costing on a model developed from the literature using an evidence based approach.

"The analytic time period consisted of 4 months of first line combination chemotherapy, subsequent cycles of secondary treatment for primary non-responders, and the progression free survival interval."(17:456).

However, they did not state the time period involved in the programme free survival, and therefore it was difficult to tell whether all relevant costs had been included in the analysis.

Licht *et al.* (1994) evaluated the impact on cost of early discharge following surgery for prostate cancer. One could argue that the follow up period of thirty days after surgery would not capture all complications or inpatient hospital stays etc.

Vetto *et al.* (1998) when looking at the cost-effectiveness of the diagnosis of breast cancer in males only looked at the costs of diagnostic procedures, and excluded any forms of follow up costs.

The above seven studies rely upon inadequate time spans for their costing procedures, and therefore significant areas of resource use and cost have been excluded from the estimation. This leads the reader to question the reliability of the results.

Quantification of resource use

Another area of importance when costing is the measurement of the resources used i.e. an assessment of the resources involved in the treatment, care or detection of the disease in question. It can be seen from Table 3.9 that the source of resource use information varies from study to study.

Table 3.9 Quantification of resource use

How resource use information was obtained	Published study
Multi-centre RCT	(14, 25, 36, 37)
Multi-centre non-randomised trial	(39)
Single centre RCT	(21, 30)
National and regional dataset	(9, 13)
Government database	(10, 11)
Case series of patients	(12, 29, 31, 33, 40, 41)
Medical records of a sample of patients	(8, 24, 26, 42-44)
Published literature	(7, 34, 45, 46)
Current practice	(16, 22)
Questionnaire	(15)
Mix of methods	(17-20, 23, 27, 28, 32, 35, 38)

The majority of studies looked at in the review based their resource use collection on single sites/centres, although a number were based on multi-centre randomised control trials(14, 25, 36, 37), or multi-centre non-randomised trials(39). Glimelius *et al.* (1995) and Gyrd-Hansen *et al.* (1998) obtained their resource use information from

randomised control trials, based on the experience of a single centre. Others used national or regional datasets, such as hospital discharge databases(32) or hospital admissions databases(13), the continuous Medicare history sample file(9). Other sources of resource-use are government databases such as the government annual spending from the US health care financing administration(10) or the Japanese ministry of health and welfare(11). Some studies used a case series of patients(12, 29, 31, 33, 40, 41), while others used medical records of a sample of patients(8, 24, 26, 42-44). Benoit *et al.* (1994), Konski *et al.* (1997), Layfield *et al.* (1993) and Shimbo *et al.* (1994) all took their resource use information from published literature(7, 34, 45, 46), while others used 'current practice' as a basis for resource use, although in all cases no information was given on what this current practice actually constituted(16, 22, 32). Lansky *et al.* (1979) used a questionnaire to ascertain resource use. A number of studies used a mixture of sources of information; Sculpher *et al.* (1995) based their resource use on the RCT and published literature, while data from a single centre RCT and medical records were used by Whynes *et al.* (1993). The cancer registry, hospital admissions database and medical records were used by Gray and colleagues (1987). Ortega *et al.* (1997) used RCT based studies and hospital charts and had the resource use verified by a panel of experts. Others used NCI patient data query, cancer registry, literature, backed up by expert advice(20), official Japanese government statistics, medical charts and expert opinion(23), trial data, literature and expert opinion(19), or trial data and hospital dossiers(27). Jones *et al.* (1994) obtained their resource use information from the Hamilton Regional Cancer Centre, Canada, using the medical

records and observation of staff and operating time by conducting interviews with staff.

Valuation of resource use information

The valuation of this resource use information should also be stated as transparently as possible. The valuation of the costs differs in respect to the source of unit cost data. For some the cost data is estimated, others used charges for procedures, while others use costs that have been published in the literature. In the review of the 40 studies, valuation of resource use was carried out in a number of ways, although two predominant methods were used; estimation (use of information on staff time, salary, capital, equipment, overheads etc.) and the use of charges (see Table 3.10).

Table 3.10 Valuation of resource use

How the resources were valued	Published study
Estimation	(8, 14-18, 20, 24, 26, 28, 30, 33, 35, 37, 39, 41)
Prices/Charges	(9, 19, 22, 25, 29, 31, 32, 36, 40, 42, 44-46)
Government expenditure	(10, 11)
Mixture of methods	(7, 12, 13, 23, 34, 38, 43)

The valuation of costs was carried out using estimation in 40 per cent of the studies. Out of these studies, very detailed and transparent estimations were carried out by Richards *et al.* (1993), Sculpher *et al.* (1995) and Wodinsky *et al.* (1987).

An example of the estimation by Sculpher *et al.* (1995) is given below:

" resource use was valued using a set of unit costs based on supplier prices or derived from the financial accounts of UCLH...The unit costs of endoscopic procedures include the costs of staff, consumables such as gloves and tubes, drugs such as sedation and reverse sedation and an allocation of hospital overheads. The cost of equipment was also included, such as the cost of the laser and of the endoscopes which has been amortised to an equivalent annual cost using a 6% discount rate, and estimates of expected useful life and annual utilisation" (18:1642).

Richards *et al.* (1993) gave a transparent and detailed account of their costing methodology (this allowed a comparison of the breast cancer cost results in this thesis with theirs, see chapter 5). The costs were split into inpatient costs, medical and surgical outpatient costs, radiotherapy costs, chemotherapy costs, surgery costs and radiology and laboratory investigation costs.

When estimating inpatient costs....

"...the cost of an overnight stay was estimated by calculating the total cost of running the ward and dividing this by the total number of overnight stays for the year 1988/89.... Salaries including employers National Insurance Contributions and London weighting for staff employed on the ward (e.g. nurses) was calculated at a March 1991 pay and price base. The proportion of the working week attributable to

the management of Breast Unit in-patients was calculated for other staff (e.g. doctors, physiotherapists, dietitians) and costs were calculated accordingly... In addition both direct (e.g. portering and domestic services) and indirect overheads (e.g. hospital administration) were included in the calculation of costs. A further 19% was added to the calculated cost to cover the capital charges applicable to Guys and Lewisham NHS trust in the year 1991-2." (26:857).

Outpatient costs were estimated in a similar fashion where they were valued as the total cost of running the clinic/ward divided by the throughput, including salary costs, consumables, portering, domestic services, administration and capital charges. Radiotherapy costs were based on published literature, chemotherapy costs and endocrine therapy costs were based on the market price of the drugs. Surgery costs were estimated by the product of length of operation and staff costs with additions for anaesthetic consumables and surgical and medical equipment, with indirect and direct overheads for running costs and capital charges. Radiology and laboratory costs included the cost of consumables, staff and direct overheads.

Wodinsky *et al.* (1987) estimated the costs using the wholesale price of the drugs, administration costs, nurses' salaries and employees benefits, consumables, dispensing fees and allocated overheads. They also considered nonmedical costs to the patients and their families, taken from published literature.

A number of studies (33 % of the total) relied on price or charges for the valuation of resource use e.g. Medicare charges, other reimbursement schedules and hospital charges (needless to say the majority of these were U.S. studies). Studies by Hodgson (1983) and Maeda (1983) used government expenditure as a proxy for cost

data. Other studies used a mixture of sources for their valuation of costs. van Ballegooijen *et al.* (1995) used a combination of Dutch hospital charges for diagnosis and treatment of cervical intraepithelial neoplasia (CIN – pre-invasive cervical cancer), and then estimated the cost of colposcopy using staff time, equipment and clinic unit costs. Norum *et al.* (1996) used a mixture of charges and national database information. Ross *et al.* (1996) produced a very comprehensive and transparent valuation of resource use using a variety of sources such as the literature, hospital finance departments, estimation using salary costs and equipment costs with amortisation over its useful lifespan. Shimbo and colleagues (1991) report use of a combination charges, literature and expert opinion. The cost of a faecal occult blood test (FOB) was taken from the Japanese national reimbursement tables, flexible sigmoidoscopy cost was taken from the literature as was the treatment cost, cost of colonoscopy and terminal illness from "expert reports", cost of follow up was based on the hospital cost of outpatient visits.

Whynes *et al.* (1993) used a mixture of estimation and previously published literature. Okubo and colleagues (1991) used the literature combined with expert opinion. Layfield *et al.* (1993 used the literature and charge data. In two of the studies reviewed it was impossible to determine the methods used for valuing the resources(21, 27).

Costs and resource-use stated separately

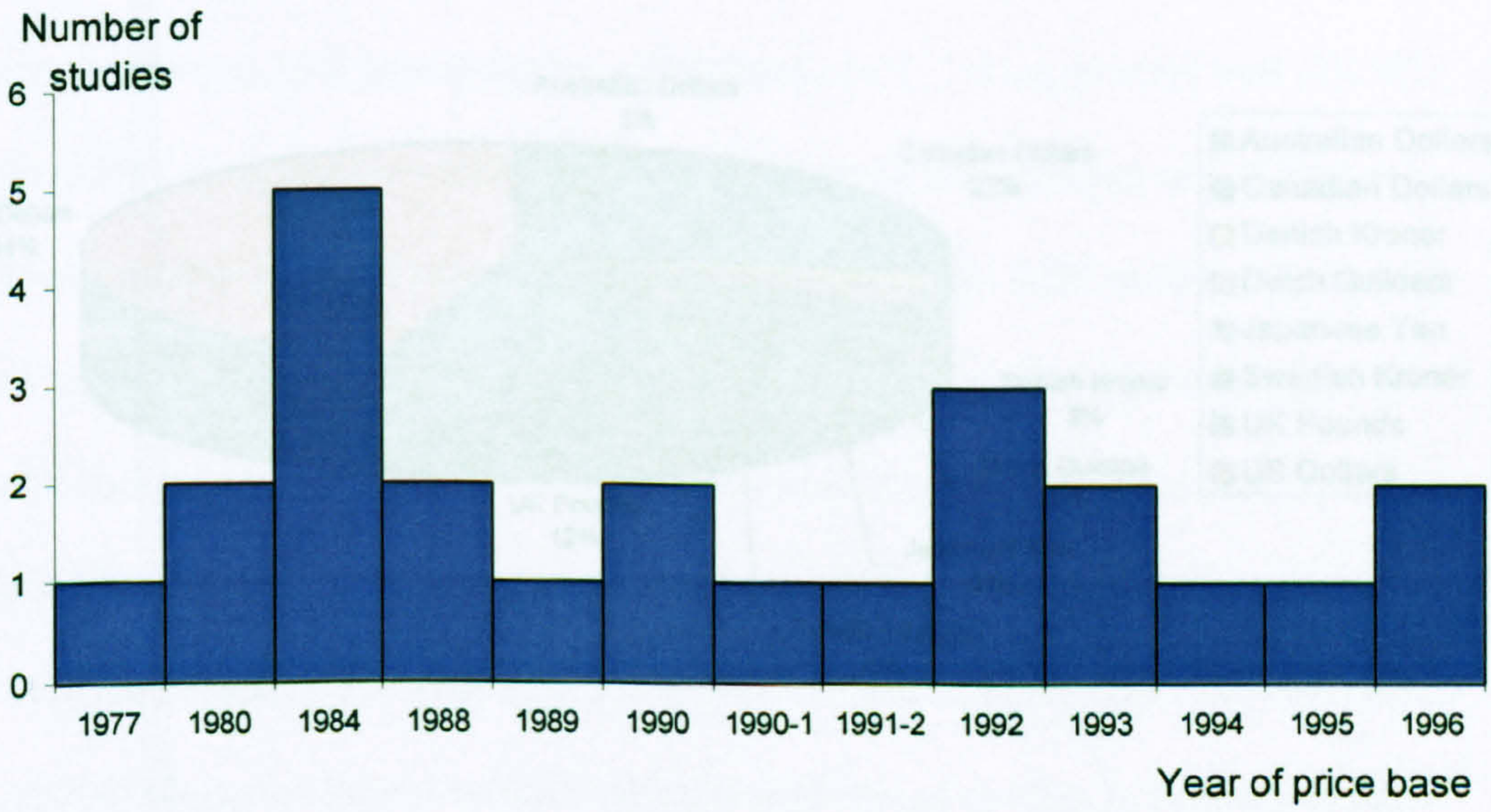
Out of the forty studies, thirteen (28 per cent) outlined the costs and quantities separately. These were displayed as either as actual numbers and percentages or average frequency counts (e.g. average number of outpatient visits) and average length

of stay. Only one paper, Gray *et al.* (1987), provide a separate analysis of the resource use data. They explore the differences in inpatient stays and survival between the intervention and control groups using a one-way analysis of variance and report F statistics and p values for these differences.

Price base

Figure 3.6 shows how the price base ranged from 1977 to 1996. Sixteen studies (40 per cent) gave no details of the price base used.

Figure 3.6 Year of price base



Index used to adjust prices

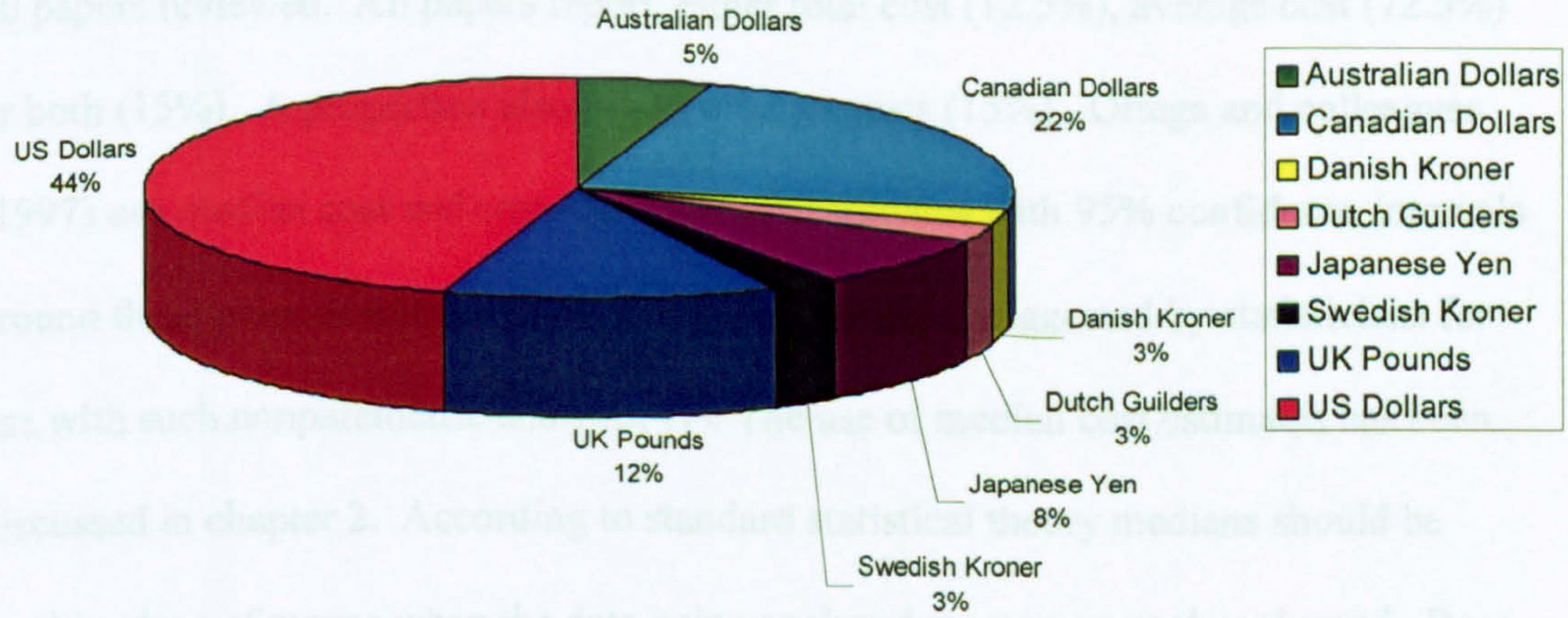
Only one study used any index to inflate the price base. Evans *et al.* (1995) used the Canadian Consumer Price Index.

Currency

The currency utilised tends to be governed by the country in which the study was carried out. Figure 3.7 reports on the currencies used.

Five studies converted their baseline currency into another currency. All five studies used exchange rates, van Ballegooijen *et al.* (1995) present the results in Dutch Guilders, but quote the exchange rate for the British pound. Two Japanese studies used exchange rates to convert yen into U.S. dollars(23, 34). Norum *et al.* (1996) converted their costs from Norwegian kroner to British pounds. Messori *et al.* (1997) report all their costs in US dollars after having converted Italian lira to U.S. dollars.

Figure 3.7 Currency used in studies



Discounting

Ten studies discounted their costs. Baker *et al.* (1991) when estimating the costs of lung and breast cancer, only discount the costs of terminal care and give no details of the discount rate used. Eight of the studies used a rate of discount of 5 per cent and one used a range of rates(12). For twelve of the studies discounting was not necessary as all the costs were incurred within one year.

Statistical analysis

Table 3.11 displays the statistical analysis and reporting of cost data undertaken for the 40 papers reviewed. All papers report, either total cost (12.5%), average cost (72.5%) or both (15%). A proportion also report median costs (15%). Ortega and colleagues (1997) use median cost and cost-effectiveness estimates with 95% confidence intervals around these point estimates, calculated using a method suggested by statisticians for use with such nonparametric analysis(47). The use of median cost estimates has been discussed in chapter 2. According to standard statistical theory medians should be used in place of means when the data being analysed are non-normal or skewed. Ross *et al*, (1996) discussed how they dealt with the problem of outliers in estimating costs of treating advanced colorectal cancer.

"*It is not uncommon for cost data to be non-normally distributed. Therefore mean treatment costs were calculated for each treatment group, as the mean accounts for the small number of patient (outliers) who generate the greatest costs.*" (43:S14)

Norum and colleagues (1996) used a slightly different approach when estimating the costs of Hodgkins disease, they noted one patient outlier who because s/he received autologous bone marrow transplantation displayed significantly higher

treatment costs than other patients in their sample. They accordingly investigated the impact on the average cost estimate of removing this patient from the analysis, the result was to reduce the average cost of stage IV patients from £29,837 to £19,943.

From the 40 published studies, 53% (21 papers) were identified as reporting patient specific resource use and /or cost data (Table 3.11). Three of the papers under the heading 'Model' also used patient-specific resource use data for their analyses (17-19). However out of a total of 24 papers using stochastic methods, only 12 (50%) of these report any measures of variation in their cost estimates. No papers in the review report confidence intervals around cost-effectiveness ratios. From the 19 papers that used stochastic data and who performed a comparison of estimated costs, only 7 used standard statistical tests to report differences in cost estimates. Two studies used one-way analysis of variance (ANOVA), 3 used the students t-test, one used the non-parametric Mann- Whitney test, and one graphically displayed average costs with 95% confidence intervals.

Table 3.11 Statistical analysis and reporting of cost data

Study	TC	AC	Per LYG	Median	Range	SD	95% CI	P value	Cost comparison and comments
Patient specific data									
Norum, 1996		✓	✓ (QALY)		✓			✓	**Comparison of cost according to four stages of Hodgkins disease using ANOVA**
Smith, 1997		✓							**Reports actual and % cost difference - no statistical test**
Lansky, 1979		✓		✓	✓	✓			**Reports average medical and non-medical costs of childhood cancer**
Glimelius, 1995		✓	✓ (QALY)			✓			**Incremental CEA between chemotherapy and best supportive care**
Raikar, 1996		✓						✓	**Comparison of costs of surgical versus endoscopic interventions for cancer of pancreas using t-test**
Gray, 1987		✓						✓	**Used ANOVA to compare home based hospice service ce. normal hospice care**
Hoffman, 1989	✓								**Reports total cost savings to a hospital of implementing a colorectal cancer screening programme**

Study	TC	AC	Per LYG	Median	Range	SD	95% CI	P value	Cost comparison and comments
Mayr, 1994	✓	✓			✓				Reports cost savings involved with implementing MRI scans for treatment planning of brain metastasis
Schapira, 1994		✓						✓	t-test of cost difference of hospice ce. no hospice care and reported SE
Agboola, 1997	✓	✓							Cost per cancer detected and incremental CEA of adding chest x-ray and smear to physical examination
Ross, 1996		✓		✓			✓		Comparison of costs of 4 chemotherapy regimens for treating colorectal cancer
Whynes, 1993		✓				✓	✓		t-test used to compare treatment costs for 4 stages of colorectal cancer
Rae, 1994		✓							Comparison of costs and cost per cancer detected for four types of faecal occult blood tests
Goodwin, 1988		✓	✓(QALY)						Incremental CEA of two different chemotherapy regimens for small cell lung cancer

Study	TC	AC	Per LYG	Median	Range	SD	95% CI	P value	Cost comparison and comments
Licht, 1994		✓							Comparison of costs of early versus late hospital discharge following surgery for prostate cancer
Jaakkimainen, 1990		✓	✓						Incremental CEA of two different chemotherapy regimens and best supportive care for non small cell lung cancer
Hanks, 1986		✓		✓	✓				Cost comparison of treating prostate cancer with surgery, lymph node dissection or radiotherapy
Kennedy, 1995		✓	✓(QALY)	✓	✓ (IQR)			✓	Incremental CEA of chemotherapy versus best supportive care for non small cell lung cancer Comparison of costs using non-parametric Mann-Witney test
Richards, 1993	✓	✓							Average cost of diagnosis and treatment of breast cancer
Messori, 1997	✓	✓	✓				✓		Incremental CEA of adjuvant therapy for melanoma

Study	TC	AC	Per LYG	Median	Range	SD	95% CI	P value	Cost comparison and comments
Vetto, 1998		✓	✓						**Reports reduction in average charges from different diagnostic procedures for breast cancer in males**
Model									
Fahs, 1992	✓	✓	✓						**Incremental CEA of one-off, annual, 3- and 5-year cervical screen compared to no-screen**
Sculpher, 1995		✓				✓			**Cost comparison of two palliative interventions for oesophageal cancer**
Shimbo, 1991		✓	✓						**Incremental cost and CEA of various screening strategies for colorectal cancer**
Gyrd-Hansen, 1998		✓	✓						**Incremental CEA of various screening strategies for colorectal cancer**
Ortega, 1997		✓	✓(QALY)	✓	✓		✓		**Incremental CEA of combination versus single agent chemotherapy for ovarian cancer**
Evans, 1995		✓							**Average cost of diagnosis, treatment and follow up of lung cancer**

Study	TC	AC	Per LYG	Median	Range	SD	95% CI	P value	Cost comparison and comments
Okubo, 1991		✓	✓						**Incremental CEA of various screening strategies for breast cancer**
Smith, 1993		✓	✓ (QALY)						**Incremental CEA of tamoxifen, chemotherapy or combined therapy for early stage breast cancer**
Layfield, 1993		✓	✓						**Incremental CEA of various diagnostic strategies for breast cancer**
Lokich, 1996	✓								**Reports monthly charges**
Other									
Jones, 1994	✓								**Incremental cost of high dose versus low dose brachytherapy**
Benoit, 1994		✓							**Reports average cost per person screened for prostate cancer by age group**
van Ballegooijen, 1995		✓							**Reports average care cost of CIN1-III**
Konski, 1997		✓							**Comparison of costs for six different treatment options for endometrial cancer**
Baker, 1991		✓							**Reports average initial, continuing and terminal care costs for breast and lung cancer**

Study	TC	AC	Per LYG	Median	Range	SD	95% CI	P value	Cost comparison and comments
Wodinsky, 1987	✓	✓		✓					Cost of outpatient versus inpatient chemotherapy
Lowenthal, 1996		✓							Cost of home- versus hospital-based chemotherapy
Hodgson, 1983	✓								COI study – cost of cancer in US
Maeda, 1983	✓								COI study – cost of cancer in Japan

Sensitivity analysis

In 48% of the studies no sensitivity analysis was undertaken. In the remainder of cases the sensitivity analysis varied in procedure. The various parameters altered include; clinical parameters, such as the natural history of the disease, progression rates, regression rates, sensitivity and specificity; the resource use parameters; cost parameters such as staff cost, equipment cost etc.; outcomes such as estimated life years, QALY, survival time and value weighting. All used one-way sensitivity analysis. Ortega *et al.* (1997) used one-way sensitivity analysis using 95% confidence intervals for given parameters, as did Sculpher *et al.* (1995). In some cases 'realistic ranges' for parameters were chosen, but very little information was given (35). In general very little information was given on why the parameters were chosen for the sensitivity analysis and where the ranges around these parameters come from. For example, Fahs *et al.* (1992) used data based on a review of the available literature, but gave no reference to the sources. Shimbo *et al.* (1991) carried out a large sensitivity analysis although again, no reference was made as to the sources of variation.

Handling missing data

Only two papers included any information on missing data, one explicitly (31). Raikar and colleagues, (1996) reported loss to follow up of 34 patients in the trial from which the resource use data for their study were obtained. However, no account was taken of this attrition in their analysis. Whynes and Walker (1993) truncate their cost data to a three-year period, so that the treatment costs were calculated for patients over a 3-year period or until death. They argue that this time period can be justified by clinical

evidence that all complications and recurrences are likely to occur within the first two years.

3.5 Conclusions

This chapter reports on the results of an initial search of the literature on cost and cancer and a detailed review of a random sample of forty of the papers detected in the search. The aim was to respond to three questions:

1. to gauge the number and nature of studies that have estimated costs with respect to the disease cancer;
2. to examine how the methods and principles of cost estimation explored in Chapter 2, transfer into practice, and;
3. to highlight the methods used and problems that may arise in the estimation and analysis of costs of cancer.

The principle findings in response to these questions are detailed below:

1. The literature search was useful in highlighting the number and type of studies undertaken by researchers when estimating the cost of different cancers and interventions for cancer. The search involves a lengthy process of scrutinizing, first, the abstracts and then the papers to determine eligibility for inclusion into the review. It was interesting to find that many of the papers detected by the search using the key search terms were of no relevance to either costing or cancer.
2. The detailed review of the forty published papers indicated that variation in the methodology used exists. For example, the design, perspective, collection of

resource use data, time horizon, source of unit cost data, analysis and reporting of results.

In the previous chapter (2), it was noted that there were some areas of current accepted conventions in costing methodology. However, when reviewing the forty costing studies, this consensus of theoretical costing conventions did not appear to be borne out in practice.

- The methods used for the measurement and valuation of resource use varied from study to study. Methods used were dependent on the nature of (in terms of retrospective or prospective, stochastic or deterministic, study perspective) and country of origin of the study.
- Where questionnaires or proformas were used to abstract resource use information, there was no indication that they had previously been piloted.
- From the review, 57.5% of the studies used a time horizon that encompassed all significant cost-generating events, 17.5% of the studies appeared to have inadequate time horizons and 25% of the studies failed to indicate the time horizon chosen for their study.
- Sixteen studies gave no details of the reference year for the cost data.
- All studies reported the currency in which the cost estimates were reported, and where currencies were converted, exchange rates were used rather than purchasing power parities.
- Twenty five per cent of the studies discounted, for the remainder, thirty per cent reported costs incurred within one year and therefore had a legitimate

reason for not discounting, while forty five per cent gave no indication of whether their costs had been discounted or not.

- Average cost estimates were reported in 88% of the studies. The remainder reported total cost estimates. Only a few of the studies explored the total budgetary impact of implementing the intervention, this was done either on a hospital or a national basis. Only 12 studies report any measures of variation in their cost estimates. No papers in the review reported confidence intervals around cost-effectiveness ratios. From the 19 papers that used stochastic data and made some comparison of estimated costs, only 7 used a formal hypothesis test using standard statistical techniques to report differences in cost estimates.
- Accounting for uncertainty and generalisability of the study in the form of a sensitivity analysis was undertaken by twenty-one of the studies, and all used one-way sensitivity analysis.

This review has therefore highlighted the fact that even where there is supposed consensus on theoretical issues involved in costing, there remains variation in practice. It is therefore unsurprising to find that new emerging techniques in costing, discussed in Chapter 2, have rarely been undertaken in practice. Most notable are the lack of reporting of the distributional form of the cost data, and the completeness of the data collected and analysed. No account was taken on the cost side for censored data in trials, and with patient-specific studies there was no mention of missing values and what was done (if anything) in these cases.

3. The review has provided a basis for the design of and methods used in the costing chapters (Chapters 5, 6 and 7) in this thesis. It has also highlighted areas of

weakness in current costing studies where further practical research is required, such as analytic methods of cost data, and issues of missing data. These areas are explored in Chapters 8 and 9 respectively.

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Appendix 3.1

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Chapter 4

Background and Methods Related to the Costing Chapters

4.1 Introduction

Cancer represents both a key public health issue and a major area of economic concern. Not only is there a high cost associated with the treatment and care needs of cancer patients but a wider social and economic loss due to premature illness and death and a cost to the patient and family in terms of time, travel and other out-of-pocket expenses. Some data are available to demonstrate this at the national level (see section 4.3). There is, however, a lack of adequate information on the cost burden at a regional and patient-specific level. This is surprising given that cancer is one of the diseases in the UK that has been relatively well documented by regional and national Cancer Registries. However UK registries have never collected data of economic consequence, for example, number and type of consultations, inpatient length of stay. UK cancer registration is discussed in more detail in section 4.6. The purpose of this thesis is to first explore the cost burden of selected cancers in the Trent region and by doing this investigate the methods used for costing these cancers.

This chapter outlines the background to the thesis, including clinical terminology, national estimates of cancer incidence, mortality and cost, and the process involved in obtaining the data. Sections 4.2 to 4.4 provide the reader with some background information essential for the thesis. This includes a description of cancer in general, the usual treatment patterns and what is meant by disease

stage. This is followed by nationally provided statistics on the current incidence, mortality and cost burdens of cancer in the UK.

Sections 4.4-4.11 outline the processes involved in obtaining the data, including the decisions made on what cancers to study, how the data were obtained, the design of the proformas for data collection and data entry. This section also provides the reader with information on the geographical region used for data collection (Trent) and the Trent Cancer Registry.

4.2 What is cancer?

The human body is made up of millions cells. Cancer occurs when one or more of the cells breaks free from the normal restraints it is under and starts to multiply in an abnormal, uncontrolled way. This can happen to more or less any type of cell (bone, blood, skin etc.) so there are as many types of cancers as there are different cells in the body- approximately 200. Unfortunately, all these cancers have different causes, symptoms and rates of progression and often respond differently to treatment.

The management of all cancers tends to be by one or a combination of four modalities. These are surgery, radiotherapy, chemotherapy and hormone therapy, all of which can either be radical or palliative depending on the disease stage.

- **Surgery** is often the first step in the treatment of cancer. The objective of surgery varies. Sometimes it is used to remove as much of the evident tumour as possible, or it may be to remove the major bulk of the tumour so that there is less that needs to be treated by other means. Depending on the cancer type and location, surgery may also provide some symptomatic relief to the patient.

- **Radiotherapy** involves the use of high-energy radiation, primarily electronically generated x-rays, to kill cancer cells. Radiation therapy works by damaging the cancer cells' DNA. Once the DNA has been damaged, the cancer cells are not able to divide and grow, causing the tumour to shrink. Equipment is used to aim high-energy x-rays or other electromagnetic radiation precisely at tumours or parts of the body where cancer cells are present. Its two main goals are to cure cancer and relieve symptoms. For many patients, radiation is the only treatment needed. However, radiation treatment may also be given in combination with chemotherapy and/ or surgery. Radiation can be used before surgery to shrink a tumour, and during or after surgery to kill any cancer cells that may still be present. Doctors sometimes use radiation along with anticancer drugs to destroy the cancer, instead of performing surgery. Radiation can also be used as a palliative therapy.

  Radiation treatment can be given in one of two forms: external or internal. Most cancer patients receive external radiation therapy where the radiation provided by a machine called a linear accelerator. This treatment is generally administered on an outpatient basis, the patient lies on a table and the beam is directed around him/her. This only takes a couple minutes, but is done five days per week for 3-6 weeks, usually at a total dose of 25-35 fractions.

  After the initial consultation, the radiation oncologist may need to do some special planning to pinpoint the treatment area, a process known as "simulation." Alignment is critical during this planning process, so the patient will be asked to lie very still on a table while the radiotherapist (a specially trained technologist), under the supervision of the radiation oncologist, uses a special x-ray machine to define the patient's treatment area, sometimes called

the treatment portal or field. This is the exact place in the body where the radiation will be aimed. Ink lines are usually drawn on the skin to identify the area to be treated. Several other treatment-planning steps occur after simulation and before treatment, but the patient is not required to be present for these. The information from simulation, other tests, and the patient's medical background will be used by the doctor, radiation physicist (who monitors the equipment), and dosimetrist (who calculates the correct dose) to create a customized treatment plan. The doctor then decides how much radiation is needed, how it will be delivered, and how many treatments the patient will need.

Internal radiation therapy places the source of the high-energy rays inside the body, as close as possible to the cancer cells. Internal radiation therapy allows the doctor to give a higher total dose of radiation in a shorter time than is possible with external treatments. The radioactive substances used typically include radium, caesium, iodine, and phosphorus, and they may be implanted for only a short time or left in place permanently. The high doses of radiation that damage or destroy cancer cells also cause side effects such as skin reactions, hair loss, nutritional problems and fatigue.

- **Chemotherapy** or the use of chemical agents to destroy cancer cells is another intervention used in the treatment of malignancies. The goal of treatment with chemotherapy has evolved from relief of symptoms to cure. A major advantage of chemotherapy is its ability to treat widespread or metastatic cancer, whereas surgery and radiation therapies are limited to treating cancers that are confined to specific areas. Almost all chemotherapy agents currently available kill cancer cells by affecting DNA synthesis or function, a process that occurs through the cell cycle. Because many chemotherapeutic agents also effect

healthy cells and organs, the patient's laboratory data should be checked before chemotherapy administration, including white blood cell count, platelet count, renal function tests, liver function tests. Abnormalities in any of these values may require dose adjustments or the delay of therapy. Additionally, pretreatment actions, such as increased fluids or administration of anti-nausea medicines may be needed to decrease side effects. The most common routes of administration for chemotherapy are by mouth, through a vein, and into a muscle.

Chemotherapy is generally spaced out over an extended period of time. Many patients receive their chemotherapy over a 4 to 12 month period of time. Additionally, the interval between doses of chemotherapy is based on achieving the greatest effect on the cancer cells, while also allowing the healing of the normal healthy cells. Most often, patients receive their chemotherapy every 3 to 4 weeks.

Combination Chemotherapy combines agents that differ in both the way they act and their side effects. This is done to achieve maximum tumour effect with minimal side effects. Because tumour cells have different biological characteristics, combining drugs may effectively eliminate cancer cells' resistance to a single agent.

Adjuvant chemotherapy may be given when no clear evidence of cancer can be found, but certain factors (e.g. metastasis to the lymph nodes) predict an increased risk of cancer recurrence.

- **Hormone therapy** aims to induce tumour shrinkage by manipulating the normal hormonal level. A number of cancer types have been found to be hormone dependent for example, breast and prostate cancers. Hormonal

therapy may consist of surgical resection to remove the source of hormone, the administration of hormonal substances or the administration of anti-hormone drugs.

4.2.1 Cancer stage

Cancers progress through well-defined stages of disease, dependent on the size and spread of the tumour. Stage generally refers to the degree to which the cancer has spread beyond its original location. Lower stages of cancer (stages I and II) are generally more confined to their site or region of origin than more advanced stages (III or IV).

Different cancer types are staged in different ways, according to a complex series of rules. While there are subtle differences in the staging rules for different cancer types, a physician generally needs to look at three things:

- **T** stage (tumour stage), defined according to the size of the tumour itself;
- **N** stage (nodal stage), defined according to the number of lymph nodes which contain cancer; and
- **M** stage (stage of metastatic disease), defined according to the presence (or absence) of cancer that has spread into other organs or parts of the body.

The TNM (tumour-node-metastases) classification is the most widely used system for classifying the extent of tumour spread(1). The T, N, and M stages have many nuances within them, and each is subdivided (T1, T2, T3, etc.) Different combinations of T, N, and M combine under the staging rules to determine whether a patient is stage I, II, III, or IV. Other staging systems exist; for example, the Dukes classification system uses stages A through to D to classify colorectal cancers. The stages A to D correspond to the stages I to IV from the TNM system.

For the purpose of this thesis all cancers are reported by stage according to this TNM classification. The ability to stage cancer accurately is of vital importance as a guide to prognosis and forms the basis upon which the initial management of the patient is decided and therefore a good indicator of the resources used and the cost of care. For all cancers the prognosis is inversely proportional to the extent of the tumour, with early stage I and II cancers having higher survival probabilities than late stage cancers III and IV. Appendix 4.1 displays the staging used for the purpose of this thesis for breast, cervical and lung cancers.

4.2.2 Grade

Cancerous cells can be 'graded' according to their degree of 'differentiation'. Differentiation refers to how closely the cancerous cells resemble their cells of origin. The more differentiated a cancer cell looks, the closer it resembles cells belonging to its organ of origin. The more undifferentiated a cell is, the less normal it looks under a microscope. In some cancers, grade can affect the cancer stage and/or impact on treatment decisions. A pathologist makes the assessment of tumour type and grade.

4.2.3 UK cancer incidence[4.1] (2-4)

With approximately 255,000 new cases registered in the UK in 1996, it is predicted that one in three people in the UK will suffer from cancer at some stage in their lifetime. However, it is more likely to occur later in life, over 65 per cent of cancers develop in those aged over 65 years old. Lung, breast, large bowel (colorectal) and prostate account for half of all new cases (Figure 4.1). The term 'other cancers' include those that contribute less than 1 percent to the total number of cancers. They include cancers of the testis, eye and gall bladder, and amount to 14% of the total UK cancer incidence.

The commonest cancer for men is lung cancer (Figure 4.2). Although the incidence has fallen as a result of a reduction in smoking in men it is still responsible for 20 per cent of all new cases. In women the most common cancer with 35,000 registrations in the UK in 1996 and accounting for a quarter of all female cancers is breast cancer (Figure 4.3). The lifetime risk of breast cancer is one in ten women. Breast cancer incidence increased throughout the 1980's, mostly occurring in screen-detected women aged 50-64 (see Chapter 5 for more detail). Similarly the number of invasive cervical cancer registrations have reduced over the past thirty years due to the National cervical screening programme, however, the number of pre-invasive cervical cancer registrations have increased over this time, with screening detecting the pre-invasive lesions (see Chapter 6).

4.1 The incidence figures reported in this thesis are not true numbers of incident cases as there are problems with coding and misclassification of cancers by the Cancer Registries. Therefore the figures reported are often an indication of the number of registrations documented by the Cancer Registries and sent to the Office for National Statistics. This is discussed in more detail in section 4.6.

4.2.4 Cancer Mortality

Cancer is the cause of a quarter of all deaths in the UK(5). In 1998 there were a total of 155,000 deaths from cancer (see figure 4.4), 23 per cent of these were attributable to lung cancer alone. Approximately half of all cancer deaths in men are caused by a combination of lung, prostate and bowel cancers (Figure 4.5). Lung cancer mortality accounts for 27 per cent of all male cancers. In women, breast and lung cancer each account for 18 per cent of all female cancer deaths (Figure 4.6). This has been due to a fall in the number of breast cancer deaths and a rise in the number of lung cancer deaths in females over the past decade. This is due to the earlier detection and better treatment of breast cancer(6, 7), combined with a rise over the past three decades in the number of female cigarette smokers. Cigarette smoking has been identified as one of the single most important causes of preventable diseases and premature death in the UK. One third of all cancer deaths are due to smoking, with 90 per cent of lung cancer deaths directly attributable to cigarette smoking(8).

4.2.4 Mortality to Incidence Ratios

Lung cancer has a high mortality to incidence ratio (0.91)(9); this is due to the poor survival rates for lung cancers. Cancers with better prognosis due to early detection or effective treatment display lower mortality to incidence ratios; colorectal 0.56, prostate 0.50, cervical 0.45, breast 0.43 and skin 0.01.

4.3 National estimates of the cost of cancer

Information on the cost of cancer is limited to estimates based on national expenditure statistics. The estimates that are often quoted are outlined below.

- Based on the bed occupancy rate by disease classification data derived from the Hospital Inpatient Enquiries of the 1980's, an estimate of the inpatient cost of cancer treatment in England and Wales was estimated to be £850 million in 1991 prices. This represents approximately 5 per cent of NHS expenditure(10) (Office of Health Economics 1992:79).

- The total costs of cancer treatment and prevention to the NHS have officially been estimated at approximately 7 per cent of health service spending(11), this represents a 1999 expenditure of approximately £3,377 million per annum

However, these estimates give no indication of cancer-specific costs, for example, lung cancer versus breast cancer. Nor do they inform decision-makers where the burden of cost lies within the treatment of specific cancers, for example, chemotherapy versus radiotherapy, or even, what costs are incurred within a specific treatment, for example, within surgery the cost of equipment, staff, consumables etc.

Figure 4.1 UK Incidence 1996: Cancers, which contribute 1% or more to total burden

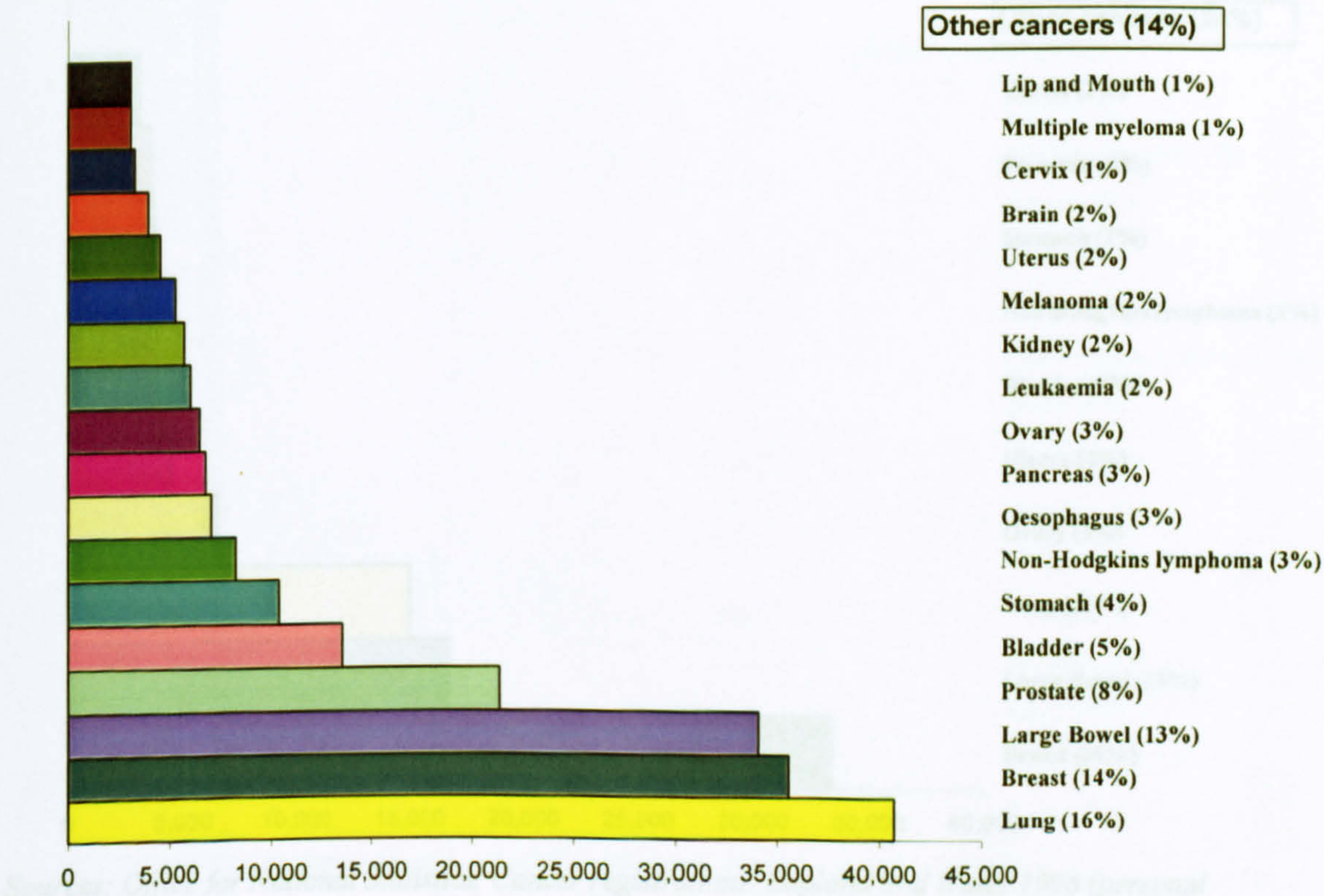


Figure 4.2 UK Incidence 1996: Males

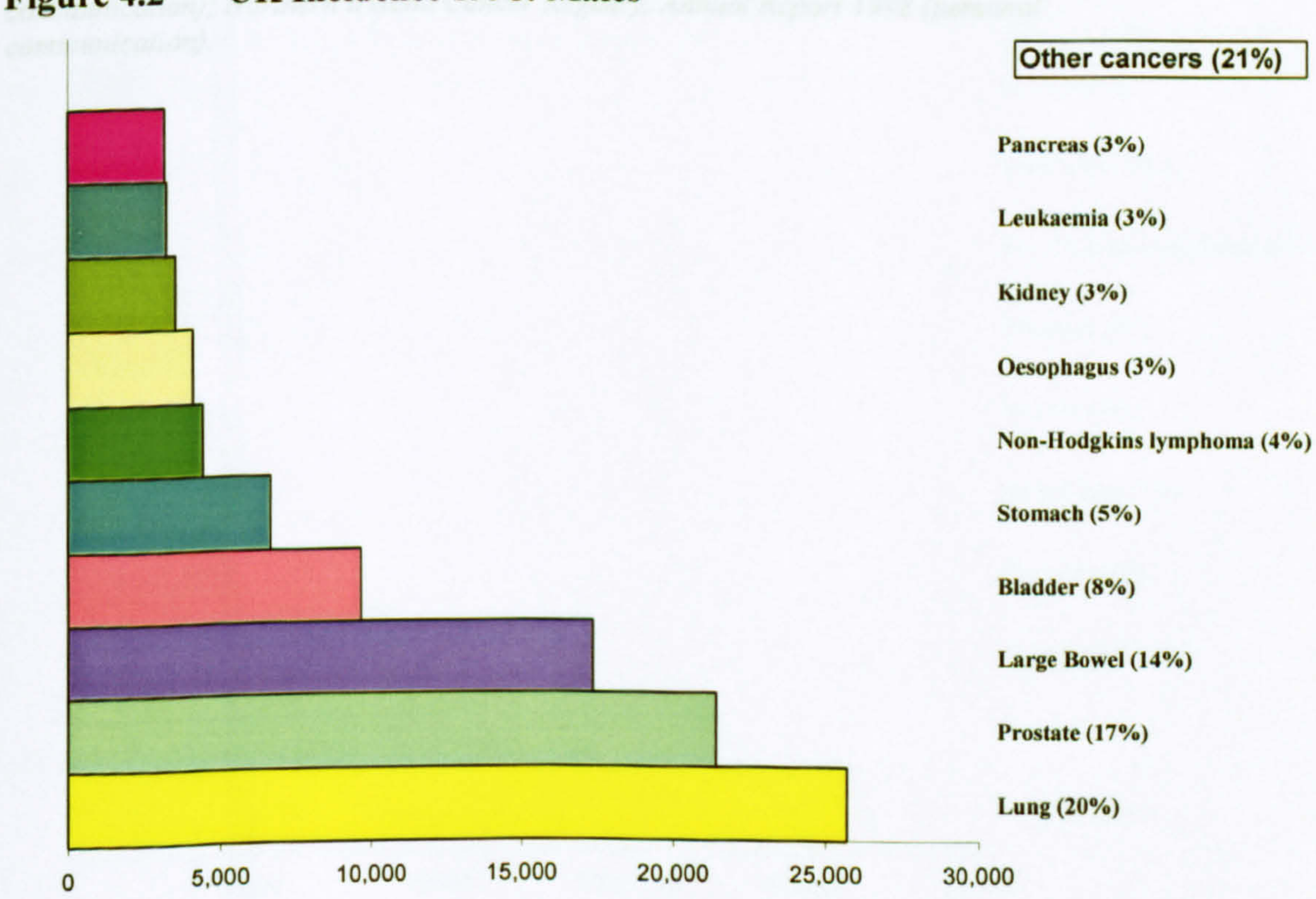
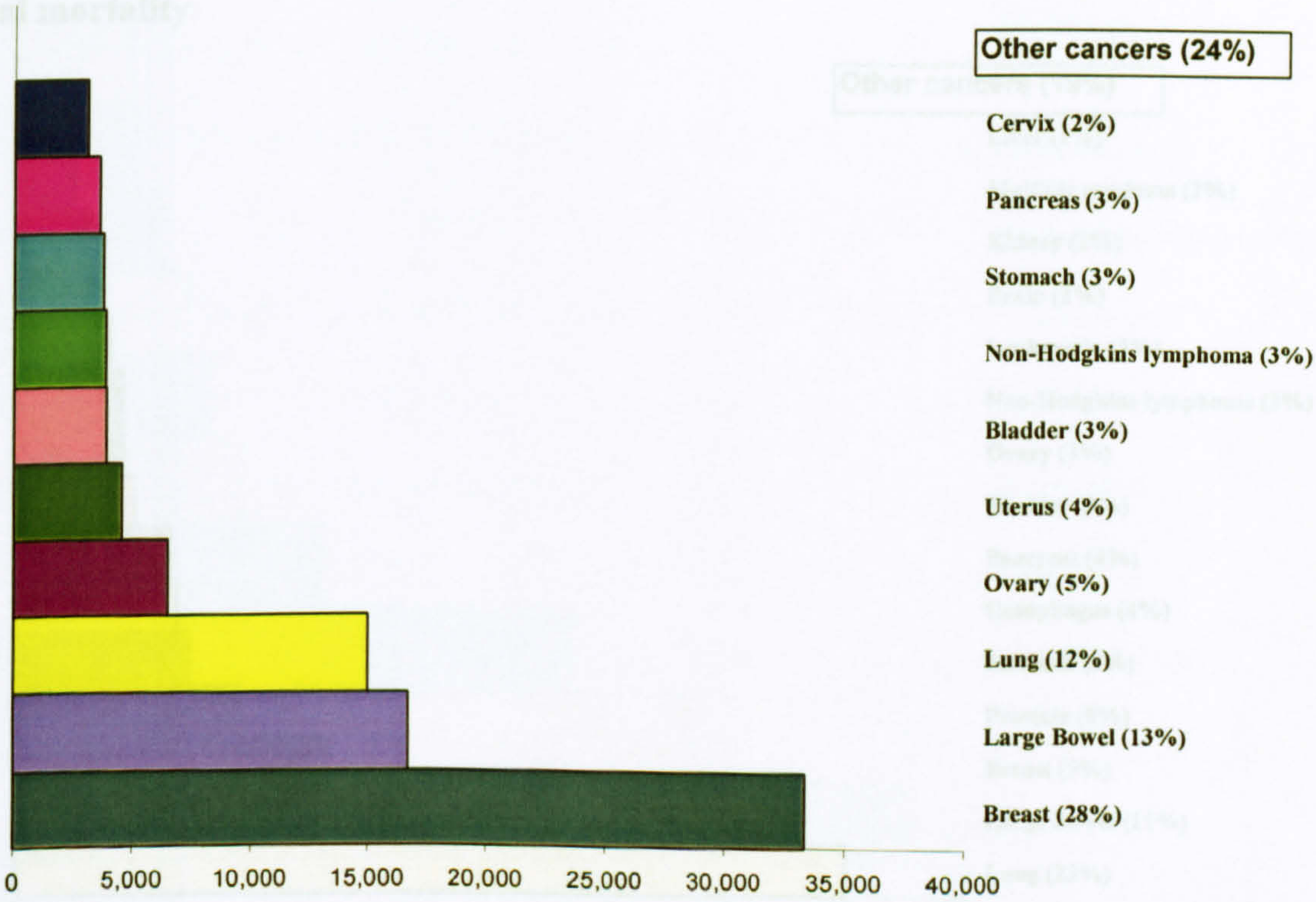


Figure 4.3 UK Incidence 1996: Females



Sources: Office for National Statistics, Cancer registrations. England and Wales 1996 (personal communication); Scottish Cancer Registry, Cancer registrations, Scotland 1996 (personal communication); Northern Ireland Cancer Registry, Annual Report 1998 (personal communication).

Figure 4.4 UK Mortality 1998: Cancers, which contribute 1% or more to total mortality

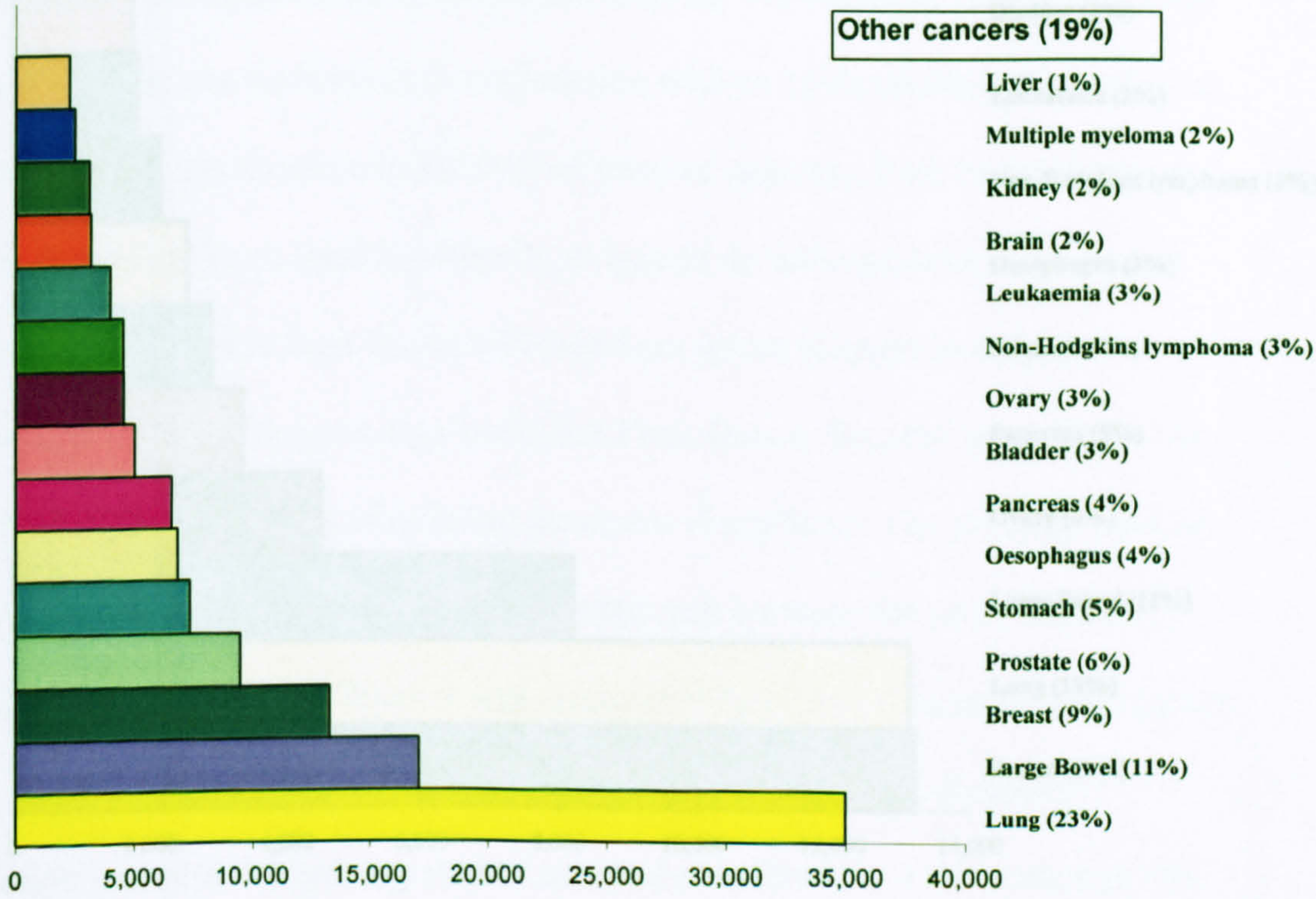


Figure 4.5 UK Mortality 1998: Males

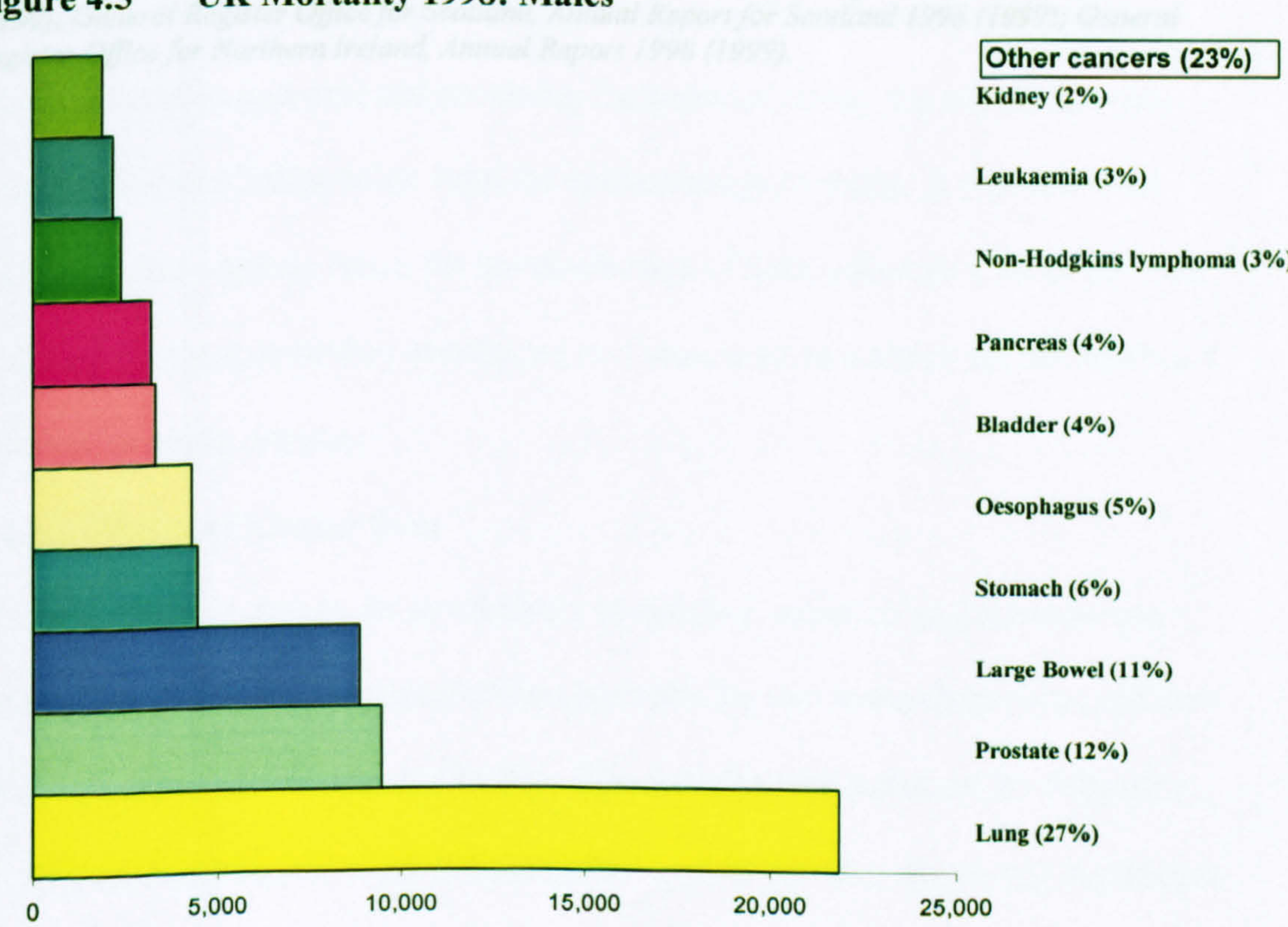
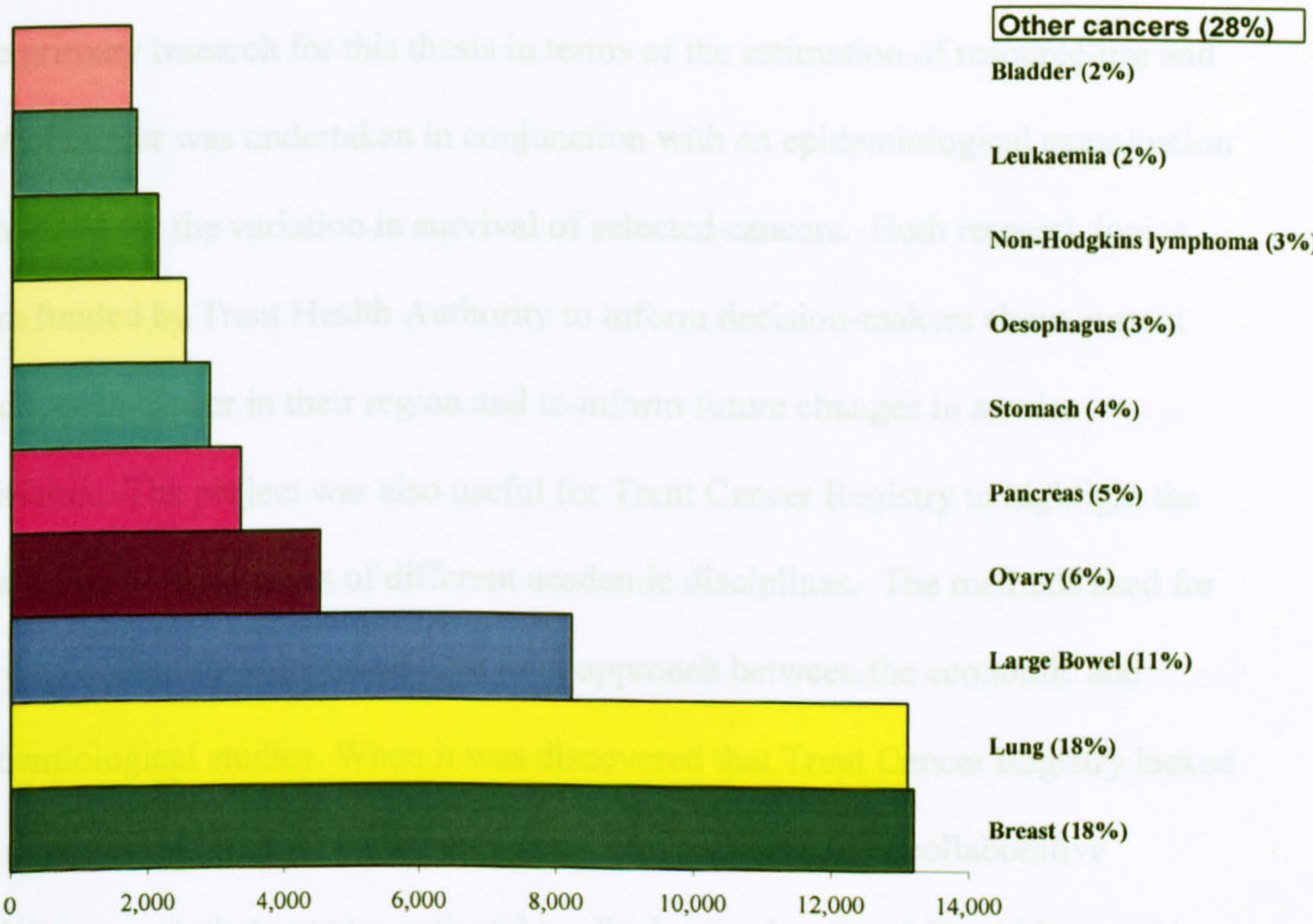


Figure 4.6 UK Mortality 1998: Females



Sources: Office for National Statistics, Mortality Statistics: Cause. England and Wales 1998 (1999); General Register Office for Scotland, Annual Report for Scotland 1998 (1999); General Register Office for Northern Ireland, Annual Report 1998 (1999).

4.4 Choice of Methods

The primary research for this thesis in terms of the estimation of resource-use and cost of cancer was undertaken in conjunction with an epidemiological examination of reasons for the variation in survival of selected cancers. Both research topics were funded by Trent Health Authority to inform decision-makers about current practices in cancer in their region and to inform future changes in service provision. The project was also useful for Trent Cancer Registry to highlight the data needs of researchers of different academic disciplines. The methods used for the data collection were based on a joint approach between the economic and epidemiological studies. When it was discovered that Trent Cancer Registry lacked the appropriate data for our research purposes (section 4.6), a collaborative decision was made to access patients' medical notes (section 4.7). Although this joint approach led to economies of scale in terms of time and cost in obtaining ethics committee approval and accessing the patients' notes, the economic study required different information from the epidemiological study. It was therefore decided to use separate forms for the abstraction of data, although a lot of the data collected for the two studies overlapped and were used as a check for the reliability of the abstraction process.

4.4.1 Choice of Cancer Sites

The three cancers chosen for the analysis of survival variation and resource-use came about due to a consensus decision between the two research projects and the funding body (Trent Health Authority). The decision was based on the following:

- The epidemiological study had identified key cancer sites displaying significant variation in survival across the region; cervix, lung, stomach and bladder.

- The health authority expressed a preference for cancers where 1) burden in terms of incidence and mortality were large, 2) the government had already set targets(11).
- For the purpose of the economic study, the requirement was 1) that no previous detailed patient specific costing had been carried out in the UK (for example, colorectal cancer was ruled out as previous patient specific costing had been undertaken(12, 13)), 2) that the cost analysis undertaken could provide useful information for future cost-effectiveness analyses of current programmes or new interventions. For example the cost analysis of breast cancer could be used in future research on the cost-effectiveness of changes to the current screening policy.

The cancers were chosen on an iterative basis, with the first site being breast cancer. Once the data collection for breast cancer was nearing an end the second site, cervical cancer was decided. Finally the third cancer (lung) was chosen when half the data collection for cervical cancer had been undertaken.

4.5 Trent Region

The setting for the research was Trent region (Figure 4.7). Trent covers the East Midlands area of England, UK. It stretches from South Yorkshire and North Lincolnshire in the north, down through Derbyshire, Nottinghamshire and the rest of Lincolnshire to Leicestershire in the south. Approximately 5 million people live in Trent, which contains both rural and urban areas, the main cities being Sheffield, Nottingham, Leicester, Derby and Lincoln (Figure 4.8).

In December 1993 the Government announced a restructuring exercise: '*Managing the new NHS in England*'. Regional Health Authorities were to be reduced from

fifteen to eight and abolished altogether in 1996, the regional tier being replaced by eight regional offices of the NHS Executive. Except for the inclusion of South Humberside, Trent region has remained unchanged geographically as a result of the 1994 re-organisation (Figure 4.9). The region has 11 health authorities responsible for assessing the health needs of their population, commissioning health services to meet those needs and working with other organisations to build healthy local communities.

Figure 4.7 Trent in relation to other Health Authorities

Figure 4.8 Trent region 1990-1994

Figure 4.9 Trent Region From 1994

4.6 Trent Cancer Registry Data

Given that cancer registrations in the UK have long been documented by the cancer registries, one might believe that the collection of patient-specific resource use information for particular cancers be easily undertaken using this pre-collected data. However, when the Trent Cancer Registry was contacted, it became clear that their core data set was rather limited in scope and lacked completeness and accuracy. For example, information on all treatment procedures, whether preventive, curative, diagnostic, investigative or palliative was essential. During the research period for this thesis, only the primary treatment procedure was documented by the Registry. The stage and grade of the cancer was unavailable, as was any information on follow-up, disease recurrence or metastatic spread. This lack of scope in the data is a problem with all Cancer Registries. Moreover, Trent Cancer Registry was trying to clear their three-year backlog of registrations. When approached in 1995 for breast cancer registration information, their most recent complete annual data were for 1991.

4.6.1 What is cancer registration?

As cancer is a major cause of illness and death in the population, it was felt to be necessary and useful to have comprehensive information about the numbers of cases of different cancers. This enables the long-term health of the population to be monitored, and aids the planning of services and care for the people affected. In order to do this effectively the cancer registration system was set up by the NHS over a 20-year period (1945-1965). In 1950 there were 74 centres registering cancer in England and Wales, by 1958 the system had been simplified and ten regional cancer registries had been set up. Full coverage of England and Wales was achieved in 1962.

4.6.2 Organisation of cancer registries

Each health region in the UK is served by a cancer registry, so that every area in the UK is covered by a cancer registry. A common set of information is collected on every case of cancer by the regional cancer registries. This is then sent into the national cancer registry, which is run by the Office for National Statistics, who conduct national monitoring of incidence, mortality and survival from cancer.

4.6.3 How is a tumour is registered

The Registry receives notifications of new tumours in a variety of ways:

Currently the most important of these is through the hospital patient administration system (PAS/HISS). A patient's records are updated on the hospital PAS/HISS when they have completed an inpatient stay or attended as a day case. If the reason for the in-patient stay is a notifiable neoplastic disease a special screen appears prompting the operator to make a cancer registration notification.

The second major source of registrations is death notifications that are routinely received for all patients for whom cancer is mentioned as a cause of death. The patient details on the death notifications are checked against the database to see whether a registration already exists for that patient. If no match is found a provisional registration is made whilst a query is sent to the patient's GP or hospital to find out whether the tumour was ever formally diagnosed and treated. If no further details about the tumour can be found other than those on the death notification then the registration for that tumour is labeled a "death certificate only" (DCO) registration.

Apart from information on registration and death, the registries collect other patient specific information (see section 4.6.5). They differ in their methods

of data collection, some employ peripatetic staff while others use hospital record staff to extract data for the registry.

4.6.4 What data are available?

Information is available on the three main areas of cancer statistics;

- incidence (how many new cases of cancer develop),
- mortality (how many people are dying from their cancer), and
- survival (how long people are living with their cancer).

The basic function of the Registry is to keep a record of every new cancer diagnosed in the population it covers. From these raw numbers of cancers the Registry calculates crude, age specific and age standardised registration rates. They are termed registration rather than incidence rates as they can never be sure that every cancer that develops is diagnosed or registered. The rates are calculated for Trent, but also for smaller areas such as the constituent district health authorities. Numbers of cancers can also be reported by hospital of initial registration or electoral ward. In addition to registration information, the Registry maintains a record of deaths from different cancers by age and sex, which it receives from the Office for National Statistics (ONS). Mortality rates are calculated from these figures. Observed and relative survival rates are calculated using survival information from the Registry database. In addition to summary numbers and rates the Registry is able to provide lists of patient specific information to authorised clients.

4.6.5 Problems with Cancer Registry data

Section 4.6 has introduced some of the problems found with using Trent Cancer Registry data for the purpose of this thesis. This section furthers this discussion,

by looking in detail at problems associated with data from all UK Cancer Registries.

- Information on completeness and accuracy of Cancer Registry data is available from specific studies(14-18). Tables 4.4-4.6 provide information on the accuracy and completeness (in terms of misclassification of cancers, differences in recorded date of diagnosis) of Trent Cancer Registry data used for the purpose of this thesis, the errors are incurred in the transition from the medical notes or hospital databases to the Registry records. However, because the selection of medical notes used for the data collection was based on registrations of patients documented by the cancer registry, the issue of whether the registry was picking up all the cancers arising in the population could not be investigated. A more recent publication has investigated this specific area of completeness(19). The researchers found that the Cancer Registry had a shortfall of 134 patients that had been listed as having cancer on a particular hospital database in 1997. The reason for this was due to the source of notifications coming from the hospital PAS system, which only documents inpatient and day case episodes , therefore excluding any patients solely managed as outpatients (such as those only treated with tamoxifen). They also found that any patient diagnosed and treated privately was missed by the registry.
- Duplication of registrations occurs between regions when a patient is resident in one region but treated in another, they can also occur due to coding error.
- For the purpose of research there are problems with the scope of the data collected by the Cancer Registry. Each Registry is required to collect a minimum set of data, however, this does not include data of economic

consequence, for example, number and type of consultations and investigations, inpatient length of stay, medication, information on recurrence, or metastases. Table 4.1 displays the data collected by Trent Cancer Registry in 1994. The lack of information required for a thorough costing exercise is clear[4.2]. In 1996, Trent Cancer Registry introduced their new minimum data set (Table 4.2 (changes highlighted in red)). Noticeable additions are the stage and grade of tumour, information on screening history and treatment indicators. Trent Cancer Registry was responding to national minimum standards and targets for registration services introduced by the NHS Executive in 1996 and the Calman report *'A Policy Framework for Commissioning Cancer Services'* that stressed the need for more stringent evaluation of cancer services(20). Hence the requirement for current practices to be documented to provide a baseline so that future services could be compared and evaluated. However, even this extended data set would be considered inadequate to provide an estimate of the cost of care for specified cancer sites.

4.2 During the process of this thesis I was consulted by Trent Cancer Registry to find out what I felt should be included in their minimum data set and what other information would be useful for the purpose of this type of costing exercise. Appendix 4.2 outlines my suggestions for a necessary minimum data set and useful extra information.

Table 4.1 Trent Cancer Registry Minimum Data Set (1994)

HOSPITAL DETAILS

- District Health Authority
- Hospital
- Consultant
- Patient Unit Number
- Radiotherapy Treatment Number

PERSONAL DETAILS

- NHS Number
- Forenames
- Surname
- Address at time of diagnosis
- Post Code
- Sex
- Marital status
- Date of birth

DIAGNOSTIC DETAILS

- Site of primary neoplasm (or main presenting secondary when primary site is not known)
- Morphology (type of neoplasm)
- Date of diagnosis (Anniversary date)
- First treatment procedure
- Date of Death

Table 4.2 Trent Cancer Registry Minimum Data Set (2000)

HOSPITAL DETAILS

- District Health Authority
- Hospital
- Consultant
- Patient Unit Number
- Radiotherapy Treatment Number

PERSONAL DETAILS

- NHS Number
- Forenames
- Surname
- Name at birth (previous surname)
- Address at time of diagnosis
- Post Code
- Sex
- Marital status
- Ethnic origin
- Date of birth
- Country of birth

OCCUPATION DETAILS

- Patient's occupation
- Patient's employment status
- Patient's industry

(for females and children aged 16 and under, head of household's occupation and industry is also recorded)

DIAGNOSTIC DETAILS

- Site of primary neoplasm (or main presenting secondary when primary site is not known)
- Morphology (type of neoplasm)
- Laterality (side) for paired organs
- Stage (for breast and cervix from 1993, colon and rectum 1995, others sites to be phased in later)
- Grade of tumour (degree of differentiation)
- Basis of diagnosis (Histology, Cytology, Haematology, Clinical Opinion, Other Tests)
- Date of diagnosis (Anniversary date)
- Treatment indicators (Surgery, Radiotherapy, Chemotherapy, Hormone Therapy, Other)
- Alive/dead
- Date of Death
- Cause and place of death (from 1996)
- Post Mortem
- Registration at Screening (breast and cervix at present)

4.7 Data collection from patient medical notes

Given the limitations with the Trent Cancer Registry data it was decided that information on resource-use and patient characteristics would have to be obtained by accessing information held in patient's medical notes. This process required local ethics committee approval for all possible districts where primary treatment was undertaken. This was sought and approved by the following local ethics committees under the proviso that the patients' consultants should be contacted to ask for permission to access their medical notes, and that they would have the final say on whether their patients' case notes could be accessed. All the consultants contacted gave their consent.

- North Lincolnshire
- South Lincolnshire
- Leicestershire
- Central Nottinghamshire
- North Nottinghamshire
- Doncaster
- Rotherham
- Barnsley
- North Sheffield
- South Sheffield
- North Derbyshire
- South Derbyshire

Patient information in the form of patient name, hospital and District Health Authority of primary treatment, consultant, patient unit number, NHS number and

radiotherapy treatment number were supplied by Trent Cancer Registry. Once consultant approval had been obtained, a corresponding list of these patient identifiers were sent to the medical records centre of the various hospitals where primary treatment had been undertaken to enable the correct case notes to be identified and 'pulled'. Each of the hospitals that had been identified as a site of primary treatment for a patient in the sample had to be visited. Over the course of the research this amounted to 24 different hospitals. Some hospitals were the site of primary treatment for all three cancer sites and had to be visited on three separate occasions (see Table 4.3). A considerable amount of time was spent in the medical records centre abstracting the resource-use information from the medical records (see Table 4.4). For some hospitals (approximately 25%) the staff refused to identify and pull the medical notes. This meant that an extra amount of my time was spent searching for the notes (approximately 3 minutes per case note). For every patient who received radiotherapy, radiotherapy centres (not necessarily based at the same hospital as diagnosis or primary treatment) kept their own medical records of radiotherapy treatment received. Thus all the appropriate radiotherapy centres (6 hospitals) had to be visited to obtain these patients' radiotherapy records. Similarly, for those patients who received chemotherapy at chemotherapy units, chemotherapy medical records were kept on site (9 sites).

The hospitals where diagnosis, treatment and follow up of the patient sample were undertaken are a mix of teaching and non-teaching hospitals. Most of the care takes place at a small number of the large providers such as Louth County, St Georges, Nottingham City and University Hospitals, Doncaster Royal Infirmary, Leicester General Hospital, Leicester Royal Infirmary, Rotherham District General, Chesterfield & North Derbyshire Royal, Derby City and Derby Royal

Infirmary, Northern General Hospital and Weston Park Hospital. A number of these have since been designated specialist cancer hospitals; St Georges, Nottingham City and Weston Park Hospitals.

4.8 Patient sample

As the data collection for this thesis was undertaken alongside the data collection for an epidemiological study, the sample size was determined by results from previous work on survival variation for the epidemiological study. For the breast cancer patients, the original sample consisted of a random sample of 100 patients in each of the four districts displaying the highest and lowest survival rates in the region (North and South Derbyshire, North Lincolnshire and Rotherham) diagnosed during the period 1979-81. Similarly, a random sample of 50 breast cancer patients diagnosed in each of these four districts in 1991 were also taken. The former period was chosen to allow for an adequate follow up period, during which all resource generating events including side-effects, complications and recurrences would have occurred. The latter sample was chosen to determine whether practices in the care of patients had changed since 1979-81.

The collection of the 1979-81 case notes proved to be difficult(18). The main problem was the inaccessibility of case notes. Data collection was therefore only carried out for the first two districts. Only an average of 37 per cent of case notes could be obtained for these two districts. For both districts, a large proportion of case notes had been destroyed. This is a direct result of the policy issued by the Department of Health that case notes can be destroyed after eight years after the last contact with a patient (circular HC (89)20). The case notes of patients who had died or were last seen within the last eight years were either held

in storage off-site or kept on-site at the hospital. In North Derbyshire, 28 per cent of the records were held in off-site storage, and the ability to access these involved a cost of £3.75 per patient record. There were five sets of case notes that could not be traced, even though four of these were apparently still alive according to Cancer Registry records. The collection of the 1979-81 data for the remaining two districts was not attempted due to the poor retrieval rates for the first two districts. The retrieval of 1991 case notes was easier. A much higher rate of retrieval was achieved. Table 4.5 displays the collection of the breast cancer data for the four districts over the two time periods.

Table 4.3 Hospital sites of primary therapy, surgery, radiotherapy and chemotherapy

District	Hospital	Breast#	Cervical	Lung
Diagnosis and referring hospital				
North Lincolnshire	Lincoln County Hospital		0.8%	3.6%
	Louth County Hospital		1.7%	4.0%
	St Georges Hospital, Lincoln		0.6%	12.6%
South Lincolnshire	Pilgrim Hospital, Boston		2.5%	2.5%
	Grantham Hospital		2.2%	0.0%
	John Coupland, Gainsborough		0.3%	0.4%
	Skegness District Hospital		0.3%	0.7%
South Humber	Grimsby District Hospital		0.0%	0.4%
	Scunthorpe General Hospital		0.0%	0.4%
Leicestershire	Glenfield General Hospital		0.0%	0.4%
	Leicester Royal Infirmary		7.5%	0.0%
	Groby Rd Hospital, Leicester		0.0%	0.4%
	Leicester General Hospital		5.0%	0.0%
	Hinckley & District Hospital		0.3%	0.0%
Nottingham	Nottingham City Hospital		9.7%	12.6%
	University Hospital, Nottingham		9.4%	13.0%
	Newark General Hospital		0.3%	0.0%
	Park Hospital (private)		0.6%	0.0%
Central Nottinghamshire	Kings Mill Hospital		6.1%	0.4%
	Bassetlaw District General Hospital		3.3%	0.7%
Doncaster	Doncaster Royal Infirmary		12.2%	0.0%
	Montagu Hospital		0.0%	4.0%
Rotherham	Rotherham District General Hospital		5.5%	16.2%
Barnsley	Barnsley District General Hospital		6.9%	0.4%
Sheffield	Northern General Hospital, Sheffield		5.5%	17.3%
	Royal Hallamshire Hospital, Sheffield		0.3%	8.7%
	Weston Park Hospital, Sheffield		0.0%	0.4%
	Nether Edge Hospital, Sheffield		0.3%	1.1%
	Jessop Hospital for Women		4.4%	0.0%
North Derbyshire	Chesterfield & North Derbyshire Royal hospital		5.8%	0.0%
South Derbyshire	Derby County Hospital		8.6%	0.0%
	Heanor District Hospital		0.3%	0.0%
Surgery				
North Lincolnshire	Lincoln County Hospital	4.5%	1.3%	0.0%
	Louth County Hospital	8.4%	1.9%	0.0%
	St Georges Hospital, Lincoln	5.1%	0.6%	0.0%
South Lincolnshire	Pilgrim Hospital, Boston	0.0%	2.5%	0.0%
South Humber	Grimsby District Hospital	1.1%	0.0%	0.0%
Leicestershire	Glenfield General Hospital	0.0%	0.0%	3.3%
	Leicester Royal Infirmary	0.0%	4.4%	0.0%
	Leicester General Hospital	0.0%	7.5%	0.0%
Nottingham	Nottingham City Hospital	0.0%	13.1%	60.0%
	University Hospital, Nottingham	0.0%	9.4%	3.3%
	Park Hospital (private)	0.0%	0.6%	0.0%
Central Nottinghamshire	Kings Mill Hospital	0.0%	1.9%	0.0%
	Bassetlaw District General Hospital	0.0%	3.8%	0.0%
Doncaster	Doncaster Royal Infirmary	0.0%	11.3%	0.0%
Rotherham	Rotherham District General	26.4%	5.6%	0.0%

	Hospital			
Barnsley	Barnsley District General Hospital	0.0%	1.3%	0.0%
Sheffield	Northern General Hospital, Sheffield	0.0%	21.3%	26.7%
	Royal Hallamshire Hospital, Sheffield	0.0%	0.0%	6.7%
	Parkfield Hospital (private)	0.6%	0.0%	0.0%
	Jessop Hospital for Women	0.0%	6.3%	0.0%
North Derbyshire	Chesterfield & North Derbyshire Royal hospital	26.4%	2.5%	0.0%
South Derbyshire	Derby City Hospital	6.7%	5.0%	0.0%
	Derby Royal Infirmary	20.8%	0.0%	0.0%
Radiotherapy				
	St Georges Hospital, Lincoln	25.3%	8.5%	20.9%
	Leicester Royal Infirmary	0.0%	11.7%	0.8%
	Nottingham City Hospital	0.0%	3.1%	28.7%
	Nottingham General Hospital	0.0%	25.6%	0.0%
	Weston Park Hospital, Sheffield	45.8%	40.4%	49.6%
	Derby Royal Infirmary	28.9%	10.8%	0.0%
Chemotherapy				
	St Georges Hospital, Lincoln	38.5%	26.3%	5.9%
	Pilgrim Hospital, Boston	0.0%	0.0%	11.8%
	Nottingham City Hospital	0.0%	21.1%	5.9%
	Nottingham General Hospital	0.0%	10.5%	0.0%
	Rotherham District General Hospital	7.7%	0.0%	0.0%
	Weston Park Hospital, Sheffield	7.7%	31.6%	58.8%
	Northern General Hospital, Sheffield	0.0%	0.0%	17.6%
	Chesterfield & North Derbyshire Royal hospital	15.4%	0.0%	0.0%
	Derby Royal Infirmary	30.8%	10.5%	0.0%

Diagnosis and referring hospital is not applicable to breast cancer patients, as the only information given by Trent Cancer Registry was hospital of primary surgical treatment. This was amended for cervical and lung cancer as this was felt to be important information.

Table 4.4 Time spent abstracting information from medical notes

	Breast	Cervical	Lung
Dates of data collection	27/2/95 – 12/10/95	9/11/95 – 22/7/96	2/11/96 – 16/11/97
Number of visits to medical records (average visit = 6 hours)	26	67	55
Average number of medical notes per visit	7	6	5

Table 4.5 Retrieval of case notes – Breast cancer

	North Derbyshire	South Derbyshire	North Lincolnshire	Rotherham
1979-91				
Total sample size	100	100	-	-
Case notes retrieved	39	35	-	-
Case notes destroyed	29	63	-	-
Case notes stored off site	28	0	-	-
Untraced case notes	4	2	-	-
1991				
Total sample size	50	50	50	50
Case notes retrieved	48	49	49	49
Untraced case notes	2	1	1	1

The patient sample for cervical cancer consisted of all the patients diagnosed in the Trent region in 1990, a total of 378 patients with invasive cervical cancer. Of this original sample, 42 patients had to be excluded on the grounds of missing notes, no information in the notes, incorrect diagnosis, duplication or being diagnosed outside the chosen year of diagnosis, 1990. Table 4.6 outlines the case note retrieval for the cervical cancer patients.

For the lung cancer patients a 10% random sample of those diagnosed in the Trent region in 1993 was taken. This amounted to 290 lung cancer patients, 252 being classified as non-small cell lung cancers (NSCLC) and 38 being classified as small cell lung cancers (SCLC) by Trent Cancer Registry. It was later found at the time of data abstraction that some of the patients had been misclassified by cell type. One patient was reported to be a non-small cell type, when in fact according to their medical notes the cell type was small cell. In addition, 9 patients were reported by the Registry as being small-cell lung cancer patients, but their medical notes stated that they were non-small cell cancer patients. This resulted in a sample with 260 non-small cell lung cancers and small-cell cancers. Four districts corresponding to the best and worst lung cancer

survival rates were chosen, North Lincolnshire, Nottinghamshire, Rotherham and Sheffield. Of this original sample 37 patients had to be excluded on the grounds of missing notes, no information in the notes, incorrect diagnosis or being diagnosed outside the chosen year of diagnosis, 1993. Table 4.7 displays the results of the medical note retrieval for the lung cancer sample.

Table 4.6 Retrieval of case notes – Cervical cancer

			Excluded:				
District	**No of case notes retrieved**	**Not found**	**Duplicate**	**Recurrence**	**No information**	**Not cancer**	**Not diagnosed in 1990**
North Derbyshire	21	3	-	-	-	3	2
South Derbyshire	31	2	-	-	-	1	2
Leicester	47	4	-	-	-	4	1
N Lincs	15		1	-	-	-	-
S Lincs	15	1	-	1	-		
Bassetlaw	12	-	-	-	-	-	-
Central Notts	23	-	-	-	-	-	-
Barnsley	71	2	-	-	-	1	2
Doncaster	24	-	-	-	-	-	-
Rotherham	44	-	-	-	-	1	-
Sheffield	20	-	-	-	2	3	-
	38	3	1	1	-	-	-

Table 4.7 Retrieval of case notes – Lung cancer

	North Lincolnshire	Nottinghamshire	Rotherham	Sheffield
SCLC				
Total sample size	5	3	5	17
No diagnosis of lung cancer	-	-	-	1
Missing notes	-	-	-	2
Diagnosed outside 1993	-	-	-	1
NSCLC	-	-	-	
Total sample size	66	71	60	63
No diagnosis of lung cancer	2	-	1	1
Missing notes	5	1	7	2
No information in notes	2	-	-	-
Diagnosed outside 1993	4	2	4	2

4.9 Limitations - Generalisability of patient sample

For cervical cancer, one can assume that this group of patients is representative of other areas in the UK due to the fact that the data for this group consist of all patients diagnosed with cervical cancer in Trent in 1990. For the breast and lung cancer patients, where a sample of those diagnosed was taken, it is probable that there are limits to the generalisability. For the breast cancer patients, once exclusions are made for misdiagnosis, patients diagnosed outside 1991 and failure to stage the cancer, there are a total of 137 patients on which to base the cost analysis. This is more worrying when costs are analysed by stage because only 6 patients are diagnosed at stage IV disease. Clearly one may question whether the costs estimated from these patients are truly representative of the population of stage IV breast cancers. Similarly, with the 10% lung cancer sample, the Cancer Registry provided the data on registrations for small-cell and non-small cell lung cancer in 1993. However, as described in section 4.8, the Cancer Registry had misclassified the cell types for a proportion of the sample. Incidence of small cell

lung cancer is expected to be 20-25% of all lung cancers(21, 22), whereas in the sample provided by Trent Cancer Registry the proportion of SCLC amounted to 10%. This represents an underestimate of the expected proportion of SCL cancers in a typical population.

It should be recalled that the cost data reported in this thesis relates to the resource-use incurred by the hospital. No information was collected on the costs incurred in the community, for example costs of care while at home, visits to and from the general practitioner or community/oncology nurse or costs of community based palliative or hospice care (only inpatient hospital based palliative care has been included in this analysis). However, with cancer care, it is the secondary care costs that dominate, GP care of cancer patients is minimal:

"... the GP's involvement with cancer diagnosis and treatment is frequently limited" Royal College of General Practitioners (1986:25).

Even follow up care is organised through the hospitals(24, 25). In addition, there is an argument against including the costs of community hospice care, the resources used are not condition specific and therefore there is enormous variation between patients. This variability arises due to the nature of care received at hospices; some patients will simply require respite care, while others will be in need of long-term care. Although no information was collected on the cost to the patient and their family in terms of time and travel costs as a direct result of receiving hospital based care, estimates of these types of costs from previous studies have been included in the analysis. This is described in more detail in each of the costing chapters (Chapters 5, 6 & 7).

4.10 Questionnaire (abstract form) design

Data were collected from the hospital case notes using a data abstract form. This was designed for all three cancer sites using reviews of the literature on the epidemiology of the cancer and its diagnostic, treatment and follow up procedures. Advice from a consultant breast cancer surgeon, a consultant radiotherapist, a consultant oncologist, a consultant thoracic surgeon and a consultant gynaecologist was also extremely useful. It permitted details of diagnostic procedures, treatment, stage of disease, and other prognostic factors, follow up and outcome to be recorded for each patient. Each of the questionnaires was piloted on a total of 30 case notes per cancer site, which allowed for improvements to be made before commencing the actual data abstraction. The abstract forms used can be found in Appendices 5.1, 6.1, and 7.1 in the relevant chapters on breast, cervical and lung cancer.

4.11 Valuing the resources

This thesis makes use of two main sources for the unit cost data: published unit costs used in other UK based studies and cost data from the hospital finance departments. An example of the unit cost data collected from the finance departments for cervical cancer is displayed in Appendix 4.3. This was performed for all three cancers. A letter was sent to each of the finance directors of the hospitals where diagnosis or treatment for patients in the sample had taken place. This letter explained the nature of the research and the unit cost data required (see Appendix 4.4). The letter was followed up a week later by a telephone call to confirm that the letter had been received and the information requirements understood. Eight of the twenty finance departments contacted asked to arrange a

meeting so that I could explain my unit cost data requirements in more detail.

Since 1993, all NHS providers have been required to follow a uniform accounting protocol, requiring that their services be costed at full cost, i.e. all service-specific variable costs, with the inclusion of the relevant components of fixed and overhead cost(26). The unit cost data collected from the hospital finance departments were pooled to provide average unit cost data across the region. Although, disagreement exists about the extent to which both centre-specific resource-use and centre-specific unit cost data need to be collected from all centres in a multi-centre study, many commentators have argued that calculation of centre-specific unit costs may not be necessary if detailed resource-use data have been collected, and may in fact conceal differences in resources utilized(27-29).

All costs were reported in the year in which diagnosis occurred, 1991 for breast cancer costs, 1990 for cervical cancer costs and 1993 for lung cancer costs. The Hospital and Community Health Services Pay and Price Index was used to inflate or deflate the cost data according to the year required(30). All costs incurred beyond the initial year of diagnosis were discounted at a rate of 6 per cent in line with current recommendations(31).

4.12 Data entry and analysis

The data from the medical notes were entered into a database using Dbase IV software, this can be exported directly into Excel, which was accordingly used for data manipulation and attaching unit costs to the resource-use data. All statistical analyses were carried out using SPSS for Windows versions 6, 8 and 9. The resource use and cost data are reported separately. The resource use data are presented by way of the number and percentage of investigations undertaken by stage and year incurred. The cost data are reported as total cost and mean cost by stage at diagnosis for the three cancer sites. Standard deviations and 95% confidence intervals are used to represent the variance of the data. The differences between the stage-specific costs are explored using a one-way analysis of variance (ANOVA). Although resource use data for the breast and cervical cancer sample are collected for up to a maximum of 60 months and 77 months (respectively) following diagnosis, the analysis is restricted to 4- and 5-year cost estimates. These time frames were chosen to reflect clinical advice on the period from diagnosis in which the majority of recurrences would be likely to occur. However, for a proportion of the breast and cervical cancer patient samples the resource-use data for the complete period of analysis were missing. This was handled using the method used by Rutten van Molken *et al.* (1994), where resources utilized in the previous months are carried forward and used for those individuals where data are missing, the *'patient-year approach'*(32). This was not an issue for the lung cancer sample as all patients have complete cost histories, either from diagnosis to death or to the 48th month of follow up.

4.13 Conclusions

This chapter has provided the background information necessary for the understanding of the following three chapters on breast, cervical and lung cancer costs. Descriptions of the disease cancer, including stage of the disease and treatment options have been discussed, backed up by information on nationally reported statistics on cancer incidence, mortality and cost. The chapter also provides a detailed account of the processes involved in obtaining the data necessary for the research purpose of this thesis, and reports the advantages and disadvantages related to this process.

The following three chapters report the hospital-based resource use and cost data related to diagnosis, treatment and follow up of breast, cervical and lung cancer in Trent region.

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Appendix 4.1

The TNM system

The TNM system for describing the anatomical extent of disease is based on the assessment of three components:

T – The extent of the primary tumour

N – The absence or presence and extent of regional lymph node metastasis

M - The absence or presence of distant metastasis

The addition of numbers to these three components indicates the extent of the malignant disease; T0, T1, T2, T3, T4

N0, N1, N2

M0, M1

Breast - Clinical TNM staging

T - PRIMARY TUMOUR

T0 No evidence of primary tumour
T1 Tumour ≤ 2cm in greatest dimension
T2 Tumour > 2cm but ≤ 5cm in greatest dimension
T3 Tumour > 5cm in greatest dimension
T4 Tumour of any size with direct extension to chest wall or skin

N - REGIONAL LYMPH NODES (same side)

N0 No regional lymph node metastasis
N1 Metastasis to palpable and mobile axillary nodes
N2 Metastasis to palpable and fixed axillary nodes
N3 Metastasis to internal mammary lymph nodes (oedema of the arm)

M - OTHER METASTASES

M0 None found
M1 Present

Stage Grouping

Stage I
T1, N0, M0
T2, N0, M0

Stage II
T1, N1, M0
T2, N1, M0

Stage III
Any T, N2, M0
Any T, N3, M0
T3, N0, M0
T3, N1, M0
T4, N0, M0
T4, N1, M0

Stage IV
Any T, any N, M1

Cervical - Clinical TNM staging

T - PRIMARY TUMOUR

T0	No evidence of primary tumour
T1	Cervical carcinoma confined to the uterus
T1a	Preclinical invasive carcinoma, diagnosed by microscopy only
T1b	Tumour with invasive component >5mm in depth taken from the base of the epithelium and >7mm in horizontal spread
T2	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of vagina
T2a	Without parametrial invasion
T2b	With parametrial invasion
T3	Cervical carcinoma extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning of the kidney
T3a	Tumour involves the lower third of the vagina, no extension to the pelvic wall
T3b	Tumour extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning of the kidney
T4	Tumour invades mucosa of bladder or rectum and/or extends beyond true pelvis

N - REGIONAL LYMPH NODES (paracervical, parametrial, obturator, internal and external iliac, presacral and sacral)

N0	No regional lymph node metastasis
N1	Metastasis to regional lymph nodes

M - OTHER METASTASES

M0	None found
M1	Distant metastasis

Stage Grouping

Stage IA
T1a, N0, M0
Stage IB
T1b, N0, M0

Stage IIA
T2a, N0, M0
Stage IIB
T2b, N0, M0

Stage IIIA
T3a, N0, M0
Stage IIIB
T1, N1, M0

T2, N1, M0
T3a, N1, M0
T3b, N1, M0

Stage IVA
T4, any N, M0
Stage IVB
Any T, any N, M1

Lung

Lung cancer is split into two main types of disease according to the cell type:
Non-small cell lung cancer (NSCLC)
Small-cell lung cancer (SCLC)
NSCLC can be staged using TNM staging (outlined below)
SCLC can be divided into **limited disease** and **extensive disease.**
For the purpose of this thesis, lung cancer is divided simply into SCLC and NSCLC, due to the fact that no information was reported in the patient medical notes on stage of the cancer.

Clinical TNM staging

T - PRIMARY TUMOUR

T0	No evidence of primary tumour
T1	Tumour ≤ 3cm (not in main bronchus)
T2	Tumour > 3cm, involving main bronchus, 2cm or more from the carina or invading pleura or with atelectasis
T3	Tumour of any size with direct extension to chest wall, diaphragm, mediastinal pleura or tumour in main bronchus < 2cm from carina
T4	Tumour of any size invading mediastinum, heart, bones, carina or tumour with malignant pleural effusion

N - REGIONAL LYMPH NODES

N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or hilar lymph nodes
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalen or supraclavicular lymph nodes

M - OTHER METASTASES

M0	None found
M1	Distant metastasis beyond supraclavicular lymph nodes

Stage Grouping

Stage I
T1, N0, M0
T2, N0, M0

Stage II
T1, N1, M0
T2, N1, M0

Stage IIIa
T1, N2, M0
T2, N2, M0
T3, N0, M0
T3, N1, M0
T3, N2, M0

Stage IIIb
Any T, N3, M0
T4, any N, M0

Stage IV
Any T, any N, M1

Appendix 4.2

Required and desired patient information for Trent Cancer Registry

Required minimum database	Desired extra information
Already collected -	
District Health Authority	
Hospital	
Consultant	
Patient Unit Number	
Radiotherapy Treatment Number	
NHS Number	
Forenames	
Surname	
Address at time of diagnosis	
Post Code	
Sex	
Marital status	
Date of birth	
Date of diagnosis	
Date of death	
Clinical Information –	**Clinical Information –**
Cancer type	Grade
Stage at diagnosis	
Screen detected	
Metastases	
Recurrence	
Resource use –	For each inpatient, outpatient and day case episode –
Number and length of inpatient stay	Dates in which incurred
Number of outpatient visits	Medication
Number of day visits	Consultations
Diagnostic procedures	
Investigative procedures	
Treatment	

Appendix 4.3
Letter to the finance offices to obtain cost information for cervical cancer

5 December 1996

Name
Director of Finance,
Finance Department,
Hospital NHS Trust address,

Dear *Name*,

I am currently working on a research project estimating the costs of selected cancers in the Trent region. This research, funded by Trent Health Authority, involves identifying the diagnostic, treatment and follow up procedures typically used in the management of selected cancers by way of a retrospective audit of a sample of medical notes. Unit cost data is subsequently combined with this resource-use information to ascertain a total procedural cost for that particular cancer type.

I am writing to you to ask for some help and advice on the unit costs of treatments and procedures for cervical cancer.

Enclosed are details of the treatments and procedures that I require cost information on:
The first set of information gives a description of the treatments and procedures of interest to me.
The second set outlines the information I require.
On the final group of pages I have constructed a table of the treatments and procedures where you can put the corresponding cost information.

For your convenience you will find a pre-paid envelope addressed to me at the Trent Institute for Health Services Research.

I hope this does not cause too much inconvenience. If you have any questions about what I have asked for, please do not hesitate to contact me on the above telephone number.

I thank you in advance for your assistance.

Yours Sincerely,

Jane Wolstenholme. (Research Assistant)

Description of Treatment and Procedures for Cervical Cancer.

Diagnostic and Staging Techniques:

Cytological smear

Colposcopy

- Examination of the cervix by means of an endoscope.

Punch biopsy

- Removal of a small cylindrical specimen for biopsy by means of a special instrument that pierces the organ. An outpatient procedure.

Cone biopsy (conization)

- Removal of a cone-shaped part of the cervix by knife or cautery. An inpatient procedure.

Loop excision (loop diathermy)

- Passage of a high frequency electrical current through the tissue so heat is produced. This is used to cut through the malignancy. An outpatient procedure.

Dilation and curettage

Examination under anaesthesia

- Use of speculum for rectovaginal and pelvic examination.

Cystoscopy

- Use of cystoscope (type of endoscope) to view the internal surface of urinary bladder.

Chest X-ray

Intravenous pyelogram / urography

- Radiographic visualization of the renal pelvis and ureter by injection of a radioopaque liquid.

Proctoscopy

- Use of proctoscope (type of endoscope) to examine the rectum.

Sigmoidoscopy

- Use of sigmoidoscope to visualize he rectum and sigmoid flexure of the colon.

Ultrasound

CT scan

- Computed tomography scanning.

Abdominal x-ray

Kidney x-ray

Pelvic x-ray

Bone scan

<u>Surgery:</u>

Total conservative abdominal hysterectomy (no pelvic node dissection).

Radical/ Wertheims hysterectomy (pelvic lymphadanectomy)

Colostomy

<u>Radiotherapy:</u>

Intracavity radiotherapy

External beam radiation

<u>Chemotherapy:</u>

Bleomycin, ifosfamide & cisplatinum (BIP)

Doxorubicin & methotrexate

Cisplatinum & bleomycin

Carboplatin

Oophorectomy

- Either excision of an ovary, or ovarian ablation by a dose of radiotherapy.

Hormone replacement therapy

Palliative care

- Inpatient care on ward, pain relief.

Follow up and Surveillance:

Outpatient visit

Radiotherapy clinic visit

Clinical examination

Cytological smear

Bimanual palpation

Chest x-ray

Spine x-ray

Head x-ray

Abdominal x-ray

Ultrasound

CT scan

Liver scan

Bone scan

MRI scan

Intravenous pyelogram (urography)

Cystoscopy

Sigmoidoscopy

Colposcopy

Histopathology laboratory:

Cost of preparing and screening slide of cervical smear.

Biochemistry

Haematology

Appendix 4.4 Unit costs for cervical cancer procdures from finance departments

Diagnostic and Staging Techniqu	OP Prices				DC Prices				IP Prices			
	mean	min	max	median	mean	min	max	median	mean	min	max	median
Cytological smear	5.60	4.79	6.29	5.63								
	45.35	25.56	60.35	44.99								
Colposcopy	48.25	39.63	60.35	46.51	173.95	97.98	326.60	163.30	239.98	205.90	308.14	205.90
Punch biopsy	40.00	16.33	60.35	43.31	198.06	152.65	273.34	176.44	257.02	205.90	308.14	257.02
Cone biopsy (conization)	23.53	10.95	43.31	16.33	238.73	152.65	432.39	209.45	269.45	233.24	305.66	269.45
Loop excision (loop diathermy)	43.31	43.31	43.31	43.31	239.75	152.65	432.39	175.37	255.78	205.90	305.66	255.78
Dilation and curettage					199.27	130.64	298.20	175.37	221.47	176.79	305.30	182.33
Cystoscopy	39.13	16.33	61.93	39.13	178.78	124.25	289.40	152.65	194.97	157.05	232.88	194.97
Chest X-ray	9.23	5.96	13.49	9.15								
Intravenous pyelogram / urography	61.15	31.24	122.12	61.17					122.12	122.12	122.12	122.12
Proctoscopy	43.31	43.31	43.31	43.31	170.08	134.90	251.50	146.97	186.73	186.73	186.73	186.73
Sigmoidoscopy	29.82	16.33	43.31	29.82	177.02	96.56	251.50	152.65	260.77	186.73	356.42	249.96
Ultrasound	21.10	12.87	32.05	19.17								
CT scan	63.50	35.50	106.50	65.68								
Abdominal x-ray	10.26	5.96	17.86	9.15								
Kidney x-ray	27.38	6.39	73.26	19.53								
Pelvic x-ray	10.63	6.39	14.24	10.37								
Bone scan	52.55	13.46	115.03	48.26								
Surgery:												
Total conservative abdominal hysterectomy									188.85	142.71	254.77	192.27
(no pelvic node dissection)												
Radical/ Wertheims hysterectomy									195.25	142.71	278.44	195.32
(pelvic lyphadanectomy)												
Colostomy									196.26	108.54	316.43	173.95
Radiotherapy:												
Intracavitary radiation												
External beam radiation												
Chemotherapy:												
Bleomycin, Ifosfamide & cisplatinum (BIP)												
Doxorubicin & methotrexate												
Cisplatinum & bleomycin												
Carboplatin												
Oophorectomy									222.49	169.90	355.00	201.70
Hormone Replacement Therapy												
Palliative Care					163.30	163.30	163.30	163.30	205.90	205.90	205.90	205.90
Follow up and surveillance:												
Outpatient visit	37.27	19.88	49.70	36.92								
Radiotherapy clinic visit	37.63	30.53	49.70	35.15								
Clinical examination	27.84	16.33	36.92	27.44								
Cytological smear	5.60	4.79	6.29	5.63								
Chest X-ray	9.23	5.96	13.49	9.15								
Abdominal x-ray	10.26	5.96	17.86	9.15								
Kidney x-ray	27.38	6.39	73.26	19.53								
Pelvic x-ray	10.63	6.39	14.24	10.37								
Head x-ray	15.70	7.10	25.56	14.89								
Bone scan	52.55	13.46	115.03	48.26								
liver scan	38.02	13.26	109.76	26.66								
CT scan	63.50	35.50	106.50	65.68								
MRI scan	123.72	85.20	167.76	117.15								
Ultrasound	21.10	12.87	32.05	19.17								
Intravenous pyelogram/ urography	61.15	31.24	122.12	61.17								
Cystoscopy	39.13	16.33	61.93	39.13	178.78	124.25	289.40	152.65	194.97	157.05	232.88	194.97
Sigmoidoscopy	29.82	16.33	43.31	29.82	177.02	96.56	251.50	152.65	260.77	186.73	356.42	249.96
Colposcopy	48.25	39.63	60.35	46.51	173.95	97.98	326.60	163.30	239.98	205.90	308.14	205.90
Laboratory:												
Histopathology	13.66	7.81	25.56	9.89								
Cytology	8.87	4.97	20.72	5.57								
Biochemistry	4.73	1.24	8.30	4.47								
Haematology	4.97	2.49	8.41	5.04								
Microbiology	5.99	3.55	8.58	5.91								
IP day												
Palliative care												

Chapter 5

Breast Cancer

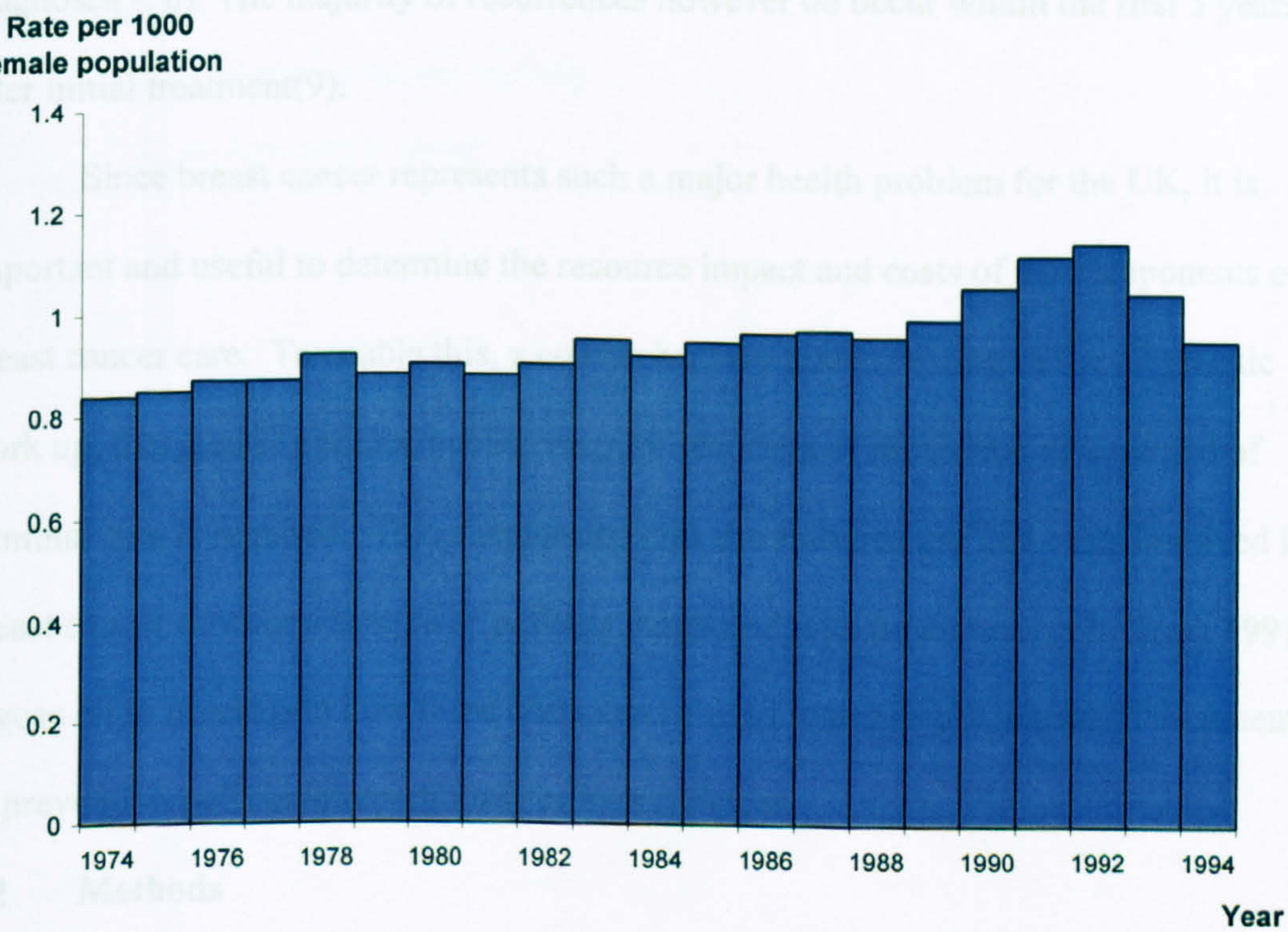
5.1 Introduction

Female breast cancer is a disease of national importance and is a major contributor to the overall level of the economic burden of cancer. It is the most common cancer in women, representing 27% of all female UK cancers. It is also the leading cause of cancer death in UK women(1). The incidence of breast cancer increased throughout the 1980's peaking in 1992. As a result an estimated 1 in 11 women will develop it in their lifetime(2).

From the most recent registration and mortality figures for England and Wales breast cancer represents:

- 31,843 new registrations in England and Wales in 1992(3).
- 2,530 new registrations in the Trent region in 1997.
- Upward trends in incidence have been noted in England and Wales over the pas decade (see Figure 5.1), although this is thought to have peaked in 1992. Sinc 1988 this increase mainly occurred in women aged 50-64 and is associated wit the national screening programme.
- 11,980 deaths from breast cancer in England and Wales in 1997; 18% of al female deaths from cancer(4).
- 1,155 deaths from breast cancer in Trent.
- Internationally, with respect to breast cancer mortality, England and Wales ar ranked fourth worst (lying behind Belgium, Scotland and Ireland) wit approximately 50 deaths per 100,000 female population (aged 35-64 years compared with Japan which has a death rate of 15 per 100,000 femal population(5).
- The 5-year relative survival rate for breast cancer in England and Wales is 64%, and for early stage breast cancer this rises to 85%, while for those with metastatic disease the 5-year survival rate is 21% These rates again compares poorly with other European countries(6).

Figure 5.1 Female breast cancer registrations 1974-1994 Trent (rate per 1000 female population)



Breast cancer strikes in the prime of life. In Trent, forty-five per cent of those diagnosed with breast cancer in 1994 were aged between 20 and 60 years of age (see Figure 5.2). Very few cases of breast cancer occur in women in their teens or early twenties, but by the age of 35-39 years over 1,000 women are diagnosed with breast cancer annually in England and Wales. The rate increases with age until it peaks with over 4,000 women aged 60-64 being diagnosed each year(3). In fact age is the most important risk factor for breast cancer. Apart from screening (secondary prevention), there is no known (primary) preventive action, as the known (hormonal) causes are not amenable to modification. Breast cancer has an unpredictable course, and although

the 5-year survival rates compared with the survival rates for other cancers are good[5.1], the risk of recurrence and metastases remains for twenty years or more after the initial diagnosis(7, 8). The majority of recurrences however do occur within the first 5 years after initial treatment(9).

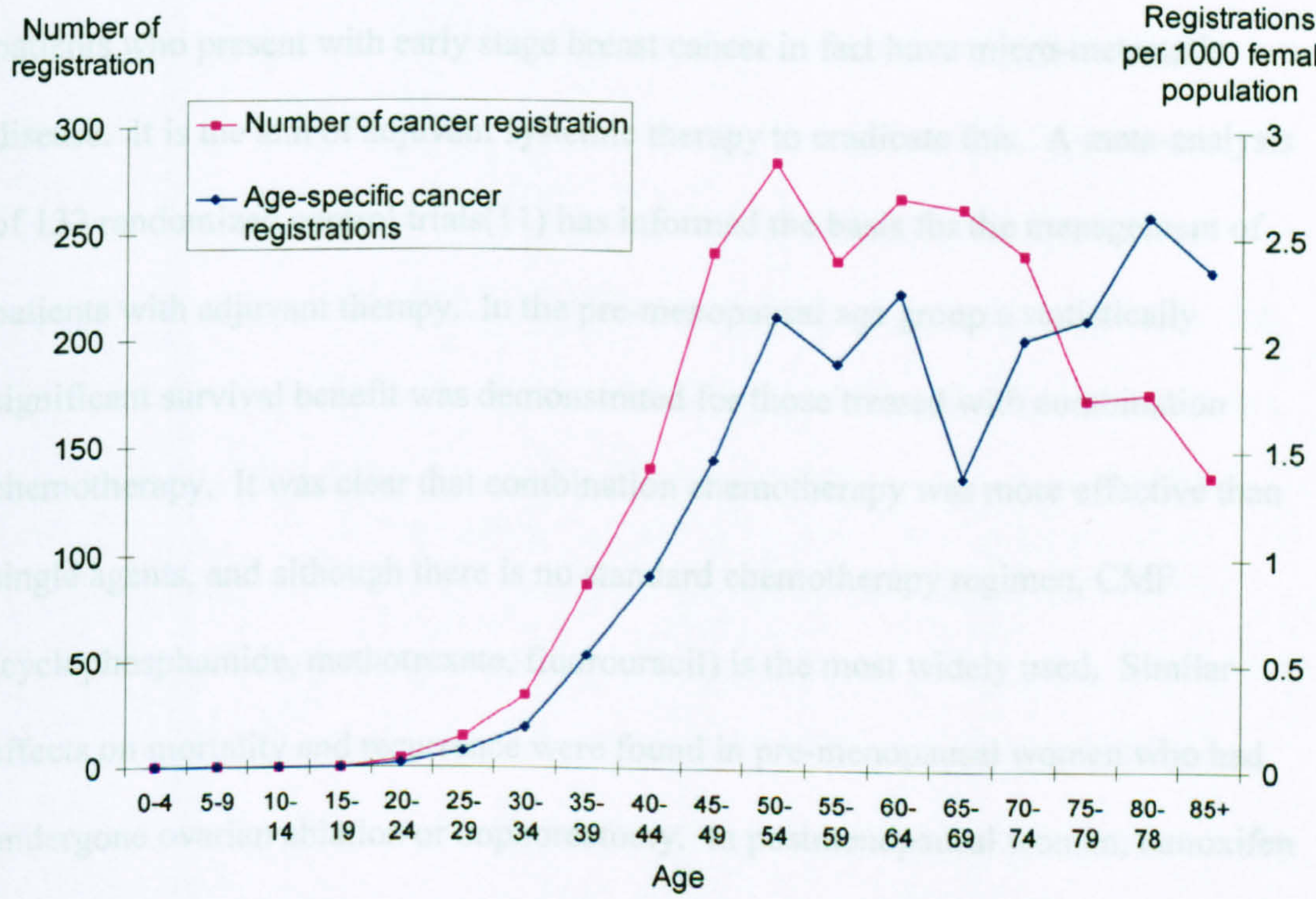
Since breast cancer represents such a major health problem for the UK, it is important and useful to determine the resource impact and costs of the components of breast cancer care. To enable this, a comprehensive understanding of the diagnostic work up, therapeutic options, management of recurrent or metastatic disease and of terminal care is required. This chapter explores the resource use and costs involved in breast cancer care for a sample of patients diagnosed with breast cancer in Trent 1991. It goes on to investigate how these costs can be used to assess the impact of treatment or prevention policies/interventions for breast cancer.

5.2 Methods

The assessment of the resource use and cost implications of breast cancer care requires data on all cost-generating events in the diagnosis, treatment and follow up of breast cancer patients. The first step was to undertake a literature search of diagnosis and treatments for breast cancer. This information was used to construct stage specific treatment algorithms (Appendix 5.1). The literature based treatment algorithms were useful in the development of an abstract form to be used for obtaining information on breast cancer resource use from the medical notes.

5.1 Approximately 64% of women diagnosed with breast cancer in 1983-85 were alive five years later (6).

Figure 5.2 Number and age-specific breast cancer registrations (Trent, 1994)



5.2.1 Treatments for breast cancer – Literature

Diagnosis: Given the suspicion of breast cancer, a confirmatory clinical diagnosis may be reached in a variety of ways. These include physical examination, mammography, fine needle aspiration, ultrasound, or any combination of these methods(10). In some circumstances the diagnostic techniques may not yield appropriate samples and therefore requires some form of excisional/tru-cut biopsy. The staging of the disease on diagnosis thereafter dictates treatment modality.

Treatment - stages I & II: For stages I and II, where the preponderance of cases are deemed potentially curable, surgery is typically employed. Such surgery might be radical (mastectomy) or conservative (lumpectomy or wide-local excision).

Thereafter, regimens of adjuvant therapy in the form of endocrine therapy, radiotherapy or chemotherapy generally follow, either singly or in combination. Many patients who present with early stage breast cancer in fact have micro-metastatic disease. It is the aim of adjuvant systemic therapy to eradicate this. A meta-analysis of 133 randomized control trials(11) has informed the basis for the management of patients with adjuvant therapy. In the pre-menopausal age group a statistically significant survival benefit was demonstrated for those treated with combination chemotherapy. It was clear that combination chemotherapy was more effective than single agents, and although there is no standard chemotherapy regimen, CMF (cyclophosphamide, methotrexate, fluorouracil) is the most widely used. Similar effects on mortality and recurrence were found in pre-menopausal women who had undergone ovarian ablation or oophorectomy. In postmenopausal women, tamoxifen was found to be beneficial, with a highly significant reduction in the annual probability of death and recurrence. Moreover, it generates fewer side-effects compared with chemotherapy. A proportion of patients will require further surgery for local or regional recurrence(12, 13).

Treatment – stage III: In comparison with cancers at stages I and II, a higher proportion of those at stage III (locally advanced) prove inoperable, requiring greater reliance upon the non-surgical therapies. The mainstay of treatment for inoperable tumours has been radiotherapy and/or tamoxifen for postmenopausal women and combination chemotherapy or ovarian ablation/oophorectomy for premenopusal women(14, 15) .

Treatment – stage IV: For stage IV patients (metastatic cancer), the principal aim of treatment is palliation of symptoms rather than cure. Treatment consists of chemotherapy and tamoxifen, with single fractions of radiotherapy given for pain relief from bone metastases(13).

Follow up: Patients with cancers at any stage risk recurrence, requiring the further employment of any or all of the modalities noted above. Due to the recurrence risk, all patients are the subjects of outpatient follow-up, entailing physical examinations, X-rays, scans, and so forth. Terminal cases from all stages may require palliative care(16, 17).

5.2.2 Estimation of treatment costs

The ideal method for costing any disease process is to have resource use and cost information on a patient specific basis. Given that the epidemiology of cancer in the UK has long been documented by the Cancer Registries on such a patient specific basis, it might be thought that a population-based resource use audit could be easily accomplished using pre-collected data. However, the Registry databases do not usually include details of either resource use or cancer stage at diagnosis. The treatment cost analysis was accordingly based on a detailed examination of the case notes of 137 breast cancer patients treated in the Trent region (central England). This was facilitated by the use of an abstract form developed with the aid of information obtained from the initial literature review on treatment (see Appendix 5.2). It was verified by a breast cancer consultant surgeon based at the City hospital, Nottingham, and piloted on 30 medical notes of breast cancer patients treated at the same hospital.

The 137 breast cancer patients used for the cost analysis were taken from an initial sample of 200 drawn at random from 4 districts covered by the Trent Cancer Registry. Of this original sample, 36 patients had to be excluded on the grounds of missing notes, incorrect diagnosis or being diagnosed outside the chosen year of 1991 (Table 5.1). Of the 164 patients who met with the inclusion criteria, for 27 (16%) there was insufficient information to enable the staging of their cancers (Table 5.2). The patient numbers were 102, 13, 16 and 6 for stages I through IV, respectively.

Table 5.1 Breast cancer sample: retrieval of medical notes and exclusion of patients (by district of primary treatment)

	District 1 N Derbyshire	District 2 S Derbyshire	District 4 N Lincolnshire	District 11 Rotherham
Number of case notes retrieved	48	49	49	49
Number not found	2	1	1	1
Excluded:				
Not able to stage	7	11	6	3
No information on breast cancer	4	3	1	3
Not diagnosed in 1991	1	3	11	3

Table 5.2 Total sample size used for cost estimation (by district of primary treatment)

	All	District 1 N Derbyshire	District 2 S Derbyshire	District 4 N Lincolnshire	District 11 Rotherham
Total sample	164	33	32	31	41
Stage I	102	25	21	21	35
Stage II	13	4	4	3	2
Stage III	16	4	2	6	4
Stage IV	6	-	5	1	-

All the patients in the sample had been diagnosed with breast cancer in 1991. This particular year was selected on the grounds that it permitted the construction of a

resource audit for each patient over a minimum of 46 months and a maximum of 60 months follow up from diagnosis, a period following diagnosis during which the majority of cancer recurrences would be likely to occur(9). The sample demographic and resource use data were entered into SPSS for Windows version 6 on a patient specific and anonymous basis. From the individual patient records, stage-specific algorithms of diagnostic and therapeutic events entailing costs were developed.

The unit costs of each event during diagnosis, treatment and follow-up were obtained from two sources. First, for events which had previously been the subject of detailed costing by other investigators (18-25), published estimates were employed, converted to 1991 prices using the National Health Service (NHS) pay and prices index. Second, for events where such data were unavailable, I requested the appropriate cost information from the finance departments of the eight service providers in the region and used the mean values obtained, again converted to 1991 prices (see Table 5.3). All costs were discounted at 6 per cent.

By combining the unit cost estimates with the resource use information, the mean costs of diagnosis, treatment and follow-up by stage at diagnosis for the sample over the follow up period were obtained. For comparative purposes costs were also split into three distinct disease phases; initial care, continuing care and terminal care costs. Initial treatment costs included all the costs initiated within the first 3 months from diagnosis and also calculated again using a longer phase of the first 6 months of treatment. Terminal care costs were calculated using the last 3 months of costs for patients who had died during the follow up period. These were also calculated again using a longer phase of the last 6 months of treatment and care. Continuing care costs

were obtained by calculating the average monthly cost incurred after the initial 3 months following diagnosis, and in cases where death occurred, prior to the final 3 months of care used for estimating the terminal care costs. Again, continuing care costs were also calculated taking account of the 6-month initial costs and 6-month terminal costs. The three month and six month periods were chosen in order to make comparisons with other studies using these time horizons(26, 27).

It is important to appreciate that, for some patients, cost over the follow up period used for this analysis will necessarily represent an under-estimate of total treatments costs arising from the condition. For those surviving, certain therapies (essentially those which are non-surgical) are likely to continue into the fifth/sixth years and beyond, and all patients will be the subjects of follow-up, usually until death. Based upon the sample data, the effects of this additional resource use can be assessed by extrapolating costs for the remaining years of life expected by patients at each disease stage.

Table 5.3 Unit Costs

Origin	Year of cost calculation	Investigation/Treatment	unit cost in 1991 prices[5.2]
Finance departments	1994/95	mammography	£22.06
		fine needle aspiration	£43.57
		tru-cut biopsy	£19.46
		frozen section biopsy	£19.47
		mastectomy	£267.97 per inpatient day
		conservative surgery	£296.02 per inpatient day
		inpatient stay	£216.58 per bed day
		out-patient visit	£74.07
		oophorectomy/ovarian ablation	£229.39
Robertson J.F.R. Whynes DK. et al.(25)	1994	biochemistry	£6.10
		haematology	£3.09
		ultrasound	£12.74
		chest x-ray	£10.10
		bone scan	£72.07
		CT scan	£63.25
		chemotherapy	
		CMF	£18.13 per month
		MMM	£236.47 per month
		epirubicin	£292.46 per month
		anti-emetics	£27.66 per month
		endocrine therapy:	
		tamoxifen (86%)	£1.34 per month
		megace (14%)	£27.57 per month
Gravelle H. et al.(21)	1980	brain scan	£16.68
		liver scan	£22.29
		marker biopsy	£45.52
Goddard M. Maher E. et al.(20)	1988	palliative radiotherapy	£46.99 per fraction
Hill F. & Oliver C. (23)	1984	palliative care	£107.85 per inpatient day

5.2 Converted to 1991 prices using the HCHS pay and price index.

Radiotherapy costs from finance departments

Radiotherapy Type	Cost per episode (£)
Low energy:	
1-4 fractions	£ 249.92
5-10 fractions	£ 624.80
Simple:	
1-4 fractions	£ 702.90
5-10 fractions	£2,093.08
11-15 fractions	£3,764.42
16-25 fractions	£5,716.92
Simple with simulation:	
1-4 fractions	£ 702.90
5-10 fractions	£2,108.70
11-15 fractions	£3,803.47
16-25 fractions	£5,763.78
Complex with simulation:	
16-25 fractions	£4,169.88
25+ fractions	£7,169.58
Complex with technical support:	
16-25 fractions	£5,873.12
25+ fractions	£7,357.02
Brachytherapy	£1,187.12

5.2.3 Survival estimates

Of the sample, 68 per cent were still alive at the time of data recording, with the result that an accurate assessment of the sample's life expectancies by stage following treatment will only be possible many years hence. However, in order to obtain life-year estimates for modelling purposes, two methods were used. The first method was to fit a trend though the survival data of the sample, to obtain mean life expectancy following treatment. Experimentation with functional forms revealed that the goodness-of-fit of complex formulations was not demonstrably superior to simple linear trends, and the latter were accordingly employed (see Appendix 5.3). For stages I and II, the survival estimates were 10.79 and 6.07 years, respectively. Owing to a

small sample size, I estimated life expectancy for those with cancers at stage III and IV on a pooled basis, resulting in an estimate of 2.53 years.

The second method used the declining exponential approximation of life expectancy (DEALE) method(28, 29). Using age and sex adjusted life expectancy figures(30) and the sample 5-year survival figures resulted in survival estimates of 10.66 years for stage I cancers, 7.49 years for stage 2 cancers and 2.03 for those with cancers at stages III and IV (see Appendix 5.3). This method was replicated using 5-year survival rates reported by the CRC in place of the sample survival rates(31). The resulting survival estimates were 12.65 years for stage I cancers, 9.59 years for stage II cancers and 5.15 years for stage III cancers and 2.45 years for those with cancers at stage IV.

Comparison of these results with national estimates of post-diagnosis survival by stage is problematic. National estimates are deemed unreliable owing to known variations in stage classification by trial centre(32). However, this estimate for early stage and later-stage cancers corresponds closely to that observed in other studies(27, 33).

Given that mean life expectancies for stage III and IV patients are less than the minimum time horizon for the data collection period (48 months), it was assumed that no additional costs would be incurred by such patients. However, patients with stage I and stage II cancers would expect to survive, and receive additional treatments, for a further 6.66 and 3.49 years on average, respectively (using the most conservative survival estimates from the DEALE method using 5-year survival data from the sample). For modelling purposes, using the method proposed by Rutten van Molken

and colleagues(34), I assumed that, for each remaining year of life, each stage I and stage II patient would consume the same quantity of therapeutic resources as she consumed, on average, in the previous 12 months. Resource use arising from diagnosis, primary surgery and radical radiotherapy was excluded from this imputed additional cost, on the grounds that these procedures are largely confined to the first two years following diagnosis. Costs of such resource use were discounted at the same rate as for the four-year calculation.

5.3 Results

5.3.1 Sample characteristics

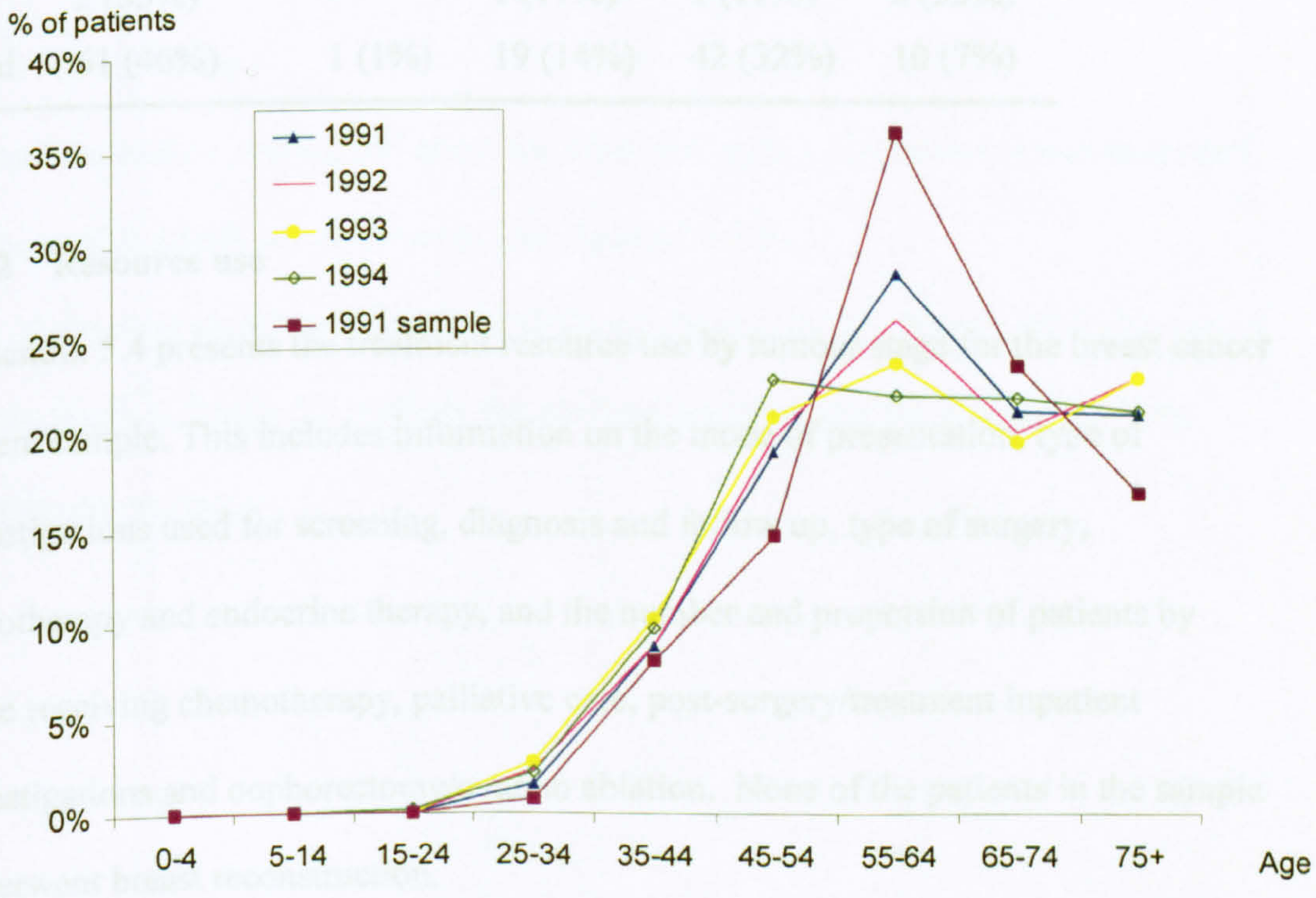
The sample characteristics by stage at diagnosis are displayed in Table 5.4.

Approximately three-quarters of the sample present with stage I disease, while less than 5 per cent present with stage IV disease. The mean age at diagnosis for the sample of patients diagnosed with breast cancer in 1991 was 62 years. A one-way analysis of variance indicates that mean age at diagnosis does not differ significantly between stage of disease ($F = 0.8301$, $P = 0.4797$). Sixty-seven per cent of the sample were still alive at the time of data collection from the medical notes, this corresponds with nationally reported 4- and 5-year survival rates(6). It can be seen from Figure 5.3 that the sample used for the cost estimation is generally representative of the Trent population of breast cancer patients in terms of age at diagnosis.

Table 5.4 Sample Characteristics

Stage	No. (%)	Mean age at diagnosis (sd)	No. deceased at abstraction (%)	No. alive at abstraction (%)
I	102 (74%)	61 (13.07)	21 (21%)	81 (79%)
II	13 (10%)	63 (12.47)	5 (38%)	8 (62%)
III	16 (12%)	63 (11.34)	14 (88%)	2 (13%)
IV	6 (4%)	69 (15.07)	5 (83%)	1 (17%)
Total	137 (100%)	62 (12.89)	45 (33%)	92(67%)

Figure 5.3 Comparison of age at diagnosis of breast cancer for sample patients (diagnosed 1991) and Trent breast cancer patients (diagnosed 1991, 1992 & 1993)



The following table (Table 5.5) depicts the mode of presentation of patients in the sample. Of the cancers in our sample 32 per cent had been detected as a result of screening, 46 per cent were self-detected, whilst the remainder were discovered primarily through examinations by general practitioners.

Table 5.5 Mode of presentation of breast cancer patients by stage at diagnosis

Stage	Self detected	Partner	GP	Screen	Other
I	43 (43%)	1 (1%)	14 (14%)	37 (38%)	5 (5%)
II	8 (61%)	-	1 (8%)	3 (23%)	1 (8%)
III	8 (53%)	-	4 (27%)	1 (7%)	2 (13%)
IV	2 (33%)	-	1 (17%)	1 (17%)	2 (33%)
Total	61 (46%)	1 (1%)	19 (14%)	42 (32%)	10 (7%)

5.3.2 Resource use

Appendix 5.4 presents the treatment resource use by tumour stage for the breast cancer patient sample. This includes information on the mode of presentation, type of investigations used for screening, diagnosis and follow up, type of surgery, radiotherapy and endocrine therapy, and the number and proportion of patients by stage receiving chemotherapy, palliative care, post-surgery/treatment inpatient investigations and oophorectomy/ovarian ablation. None of the patients in the sample underwent breast reconstruction.

From the sample;

- 90%, 92%, 57% and 0% of stage I-IV patients respectively received a primary surgical procedure.
- 40%, 62%, 38% and 33% of stage I-IV patients respectively received radical radiotherapy.
- 3%, 15%, 13% and 17% of stage I-IV patients respectively received chemotherapy.
- 92%, 100%, 94% and 100% of stage I-IV patients respectively received endocrine therapy.
- 1%, 8%, 13% and 17% of stage I-IV patients respectively received palliative radiotherapy.

To enable detailed costing and allow for discounting, this resource-use was estimated by the year in which it was incurred (see Appendix 5.5).

One of the most significant factors contributing to the cost of cancer care is the cost of hospitalization. Table 5.6 outlines the average length of stay for stages I to IV by therapeutic procedure.

Table 5.6 Inpatient length of stay by cancer stage - Breast cancer

	stage I			stage II			stage III			stage IV		
	mean	sd	(% of stage I patients)	mean	sd	(% of stage II patients)	mean	sd	(% of stage III patients)	mean	sd	(% of stage IV patients)
mastectomy	6.69	3.61	(61)	7.20	5.51	(85)	7.67	2.50	(38)	-		
conservative surgery	4.39	3.28	(38)	6.00	2.16	(23)	1.67	1.15	(25)	-		
radical radiotherapy	41.33	20.53	(3)	-			-			-		
chemotherapy	1	-	(1)	-			7.00	-	(6)	-		
palliative radiotherapy	13.50	10.61	(2)	-			-			50.00	18.38	(33)
palliative care	13.70	14.59	(12)	8.40	5.73	(38)	26.25	24.51	(50)	37.00	41.33	(50)
investigations	4.77	5.71	(13)	3.00	-	(8)	27.75	21.33	(19)	-		
complications and bone fractures.	1	-	(1)	5.00	4.24	(15)	-			2.00	-	(17)

Figure 5.4 shows the length of stay by stage for the two surgical procedures performed on the sample of breast cancer patients. For all three stages the average length of stay for those patients treated by mastectomy exceed those who underwent conservative surgery. When observing all patients who underwent some form of surgery, the mean length of stay for mastectomy patients (7 days) was longer than the mean length of inpatient stay for conservative patients (4 days) ($P = 0.001$).

Following initial treatment for the cancer significant burdens of care are again incurred when a patient suffers a recurrence or disease progression (regional recurrence or metastasis). Table 5.7 displays the recurrence and disease progression by stage of the disease at diagnosis.

Figure 5.4 Average length of stay by primary surgical procedure

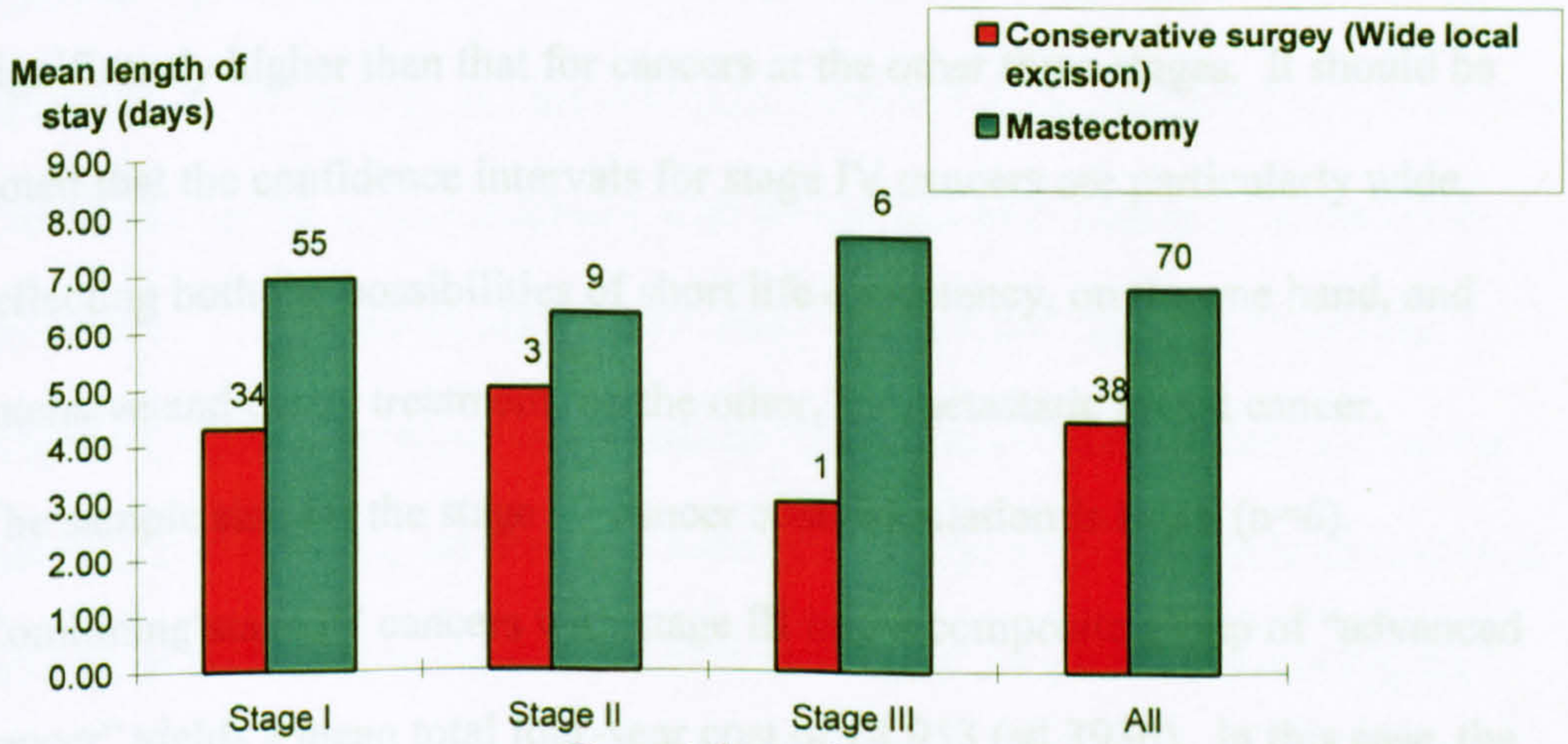


Table 5.7 **Recurrence and disease progression by stage at diagnosis for the breast cancer sample**

	All	Stage I	Stage II	Stage III	Stage IV
Local recurrence	5 (4%)	2 (2%)	1 (8%)	2 (13%)	-
Contralateral recurrence	2 (1%)	1 (1%)	1 8%)	-	-
Regional Metastasis	5 (4%)	5 (5%)	-	-	-
	37 (27%)	19 (19%)	3 (23%)	10 (63%)	6 (100%)
Site of metastasis		Liver (4) Lung (2) CNS (1) Bone (8) Pleura (1) Ascites (1) Missing info (2)	Bone (1) Brain (1) Missing info (1)	Lung (3) CNS (1) Bone (5) Missing info (1)	CNS (1) Bone (3) Pleura (1) Brain (1)

5.3.3 Treatment costs

Table 5.8 presents the results of the cost analysis. For the sample data, one-way analysis of variance (Duncan multiple range test at 5 per cent) suggests that the mean total cost of diagnosis, treatment and follow up for stage IV cancers is significantly higher than that for cancers at the other three stages. It should be noted that the confidence intervals for stage IV cancers are particularly wide, reflecting both the possibilities of short life expectancy, on the one hand, and intensive and costly treatment, on the other, for metastatic breast cancer. The sample size for the stage IV cancer cost calculation is small (n=6). Combining stage IV cancers with stage III into a composite group of "advanced cancer" yields a mean total four-year cost of £4,953 (sd 3930). In this case, the Duncan test reveals no significant differences between mean cost for cancers in stage I, stage II and the advanced cancer group. It is worth noting that although the stage IV cancer cost sample is small and displays a large standard deviation,

the difference in costs between this group of patients and the patients in other stages is still significant. Palliative radiotherapy and palliative care are the largest contributors to the overall cost of stage IV patients (table 5.8), this is unsurprising given the average length of stays for these procedures are 50 and 37 days respectively (see table 5.6).

Analysis of the costs was also carried out for the 27 cancers that could not be staged. These unstaged cancers yield an average cost of £3,066 (sd 1425), the Duncan test reveals no significant differences between mean cost of unstaged and stage I, II, and III cancers.

Treatment costs may also vary according to factors other than stage of the cancer. Other well-documented factors affecting treatment decisions in breast cancer include age and menopausal status. Table 5.9 shows that for stage I cancers both pre-menopausal women and women aged <50 years result in significantly higher costs than post-menopausal women and ≥50 year olds respectively. Moreover, for the cost information to be useful to other researchers, exploration of the costs associated with recurrence and disease progression is necessary. Table 5.10 displays such costs. These were calculated from the diagnosis of the recurrence or metastasis to the time of death or last seen at the hospital. Another way cancer costs have been analysed by other researchers is to split them according to three disease phases, initial care costs, continuing care costs and terminal care costs(26, 27). These initial, continuing and terminal care costs for the breast cancer sample have been estimated according to stage of disease and are displayed in Table 5.11.

It is useful to observe when the costs of breast cancer treatment are incurred. Figure 5.5 explores these treatment costs by year from diagnosis. In the first two years following diagnosis the average cost incurred by stage IV patients are significantly higher than those incurred by stage I-III patients. These stage IV costs fall in years 3-4, the reason being that only one stage IV patient remains alive throughout this period, and she only incurs costs associated with a normal follow up regime. Table 5.12 presents the estimates of lifetime costs, at various discount rates. Using either of the above formulations for late-stage cancers (stage III and IV separately or combined), the addition of the imputed extra costs of treatment following the initial audit period makes the differences between the mean total costs for each cancer stage statistically insignificant (Duncan test). As costs for early-stage cancer depend upon estimated life expectancies, table 5.12 also illustrates the sensitivity of early-stage cancer costs to the assumption of life expectancies one year shorter than the initial estimate and changes in the discount rate.

Table 5.8 Four-year costs of breast cancer diagnosis, treatment and follow-up, by stage (£, 1991)

	I		II		III		IV	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total cost	3,734	2,469	4,393	2,395	4,331	3,470	6,613	4,919
95% confidence intervals	3,249 - 4,219		2,946 - 5,841		2,481 - 6,179		1,450- 11,776	
	% of total cost		% of total cost		% of total cost		% of total cost	
Diagnosis	1.7		1.0		0.7		0.3	
Radical surgery	31.7		36.5		16.4		-	
Conservative surgery	13.8		10.8		2.3		-	
Endocrine therapy	1.3		1.3		0.8		0.5	
Radical radiotherapy	15.9		11.8		6.1		3.8	
Chemotherapy	1.8		3.3		5.3		4.3	
Palliative radiotherapy	1.9		0.5		1.2		53.8	
Oophorectomy/ablation	0.2		-		-		-	
Palliative care	4.5		8.2		21.7		30.3	
Inpatient stay - investigations	3.6		1.3		31.6		-	
Inpatient stay - complications	0.1		4.2		-		1.1	
Follow-up	23.5		21.1		13.9		5.9	

Table 5.9

Total cost by age (£, 1991)

	N	All		Stage I		Stage II		Stage III & IV	
Age		Mean	SD	Mean	SD	Mean	SD	Mean	SD
<50	18	5,347	2,737	5,195	2,377	6,124	2,759	5,630	6,087
50-64	64	3,254	1,849	3,235	1,931	3,814	1,170	3,022	1,753
≥65	55	4,409	3,382	3,869	2,946	4,300	2,842	6,127	4,457
		$F_{df2,134}$ = 5.404 (0.06)		$F_{df2,99}$ = 3.742 (0.03)		$F_{df2,10}$ = 0.632 (0.55)		$F_{df2,19}$ = 1.62 (0.22)	

Total cost by menopausal status (£, 1991)

	Stage I			Stage II			Stage III & IV		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Pre-menopausal	13	5,262	2,460	1	3,365	-	3	5,047	4,493
Post-menopausal	86	3,470	2,396	12	4,479	2,480	18	5,145	4,261
	t_{97} = 2.5 (0.01)			t_{11} = -0.43 (0.67)			t_{19} = -0.04 (0.97)		

Table 5.10 Costs of recurrence and disease progression

	Stage I		
	N	Mean	SD
Local recurrence	2	£1,625	184.68
Regional recurrence	5	£1,731	1064.16
Metastasis	19	£1,764	2098.42
	Stage II		
	N	Mean	SD
Local recurrence	1	£141	-
Regional recurrence	0	-	-
Metastasis	3	£786	785.8
	Stage III		
	N	Mean	SD
Local recurrence	2	£1,960	1958.4
Regional recurrence	-	-	-
Metastasis	10	£3,105	2894.03
	Stage IV		
	N	Mean	SD
Local recurrence	0	-	-
Regional recurrence	0	-	-
Metastasis	6	£6,613	4919.88

Figure 5.5 Treatment cost by year

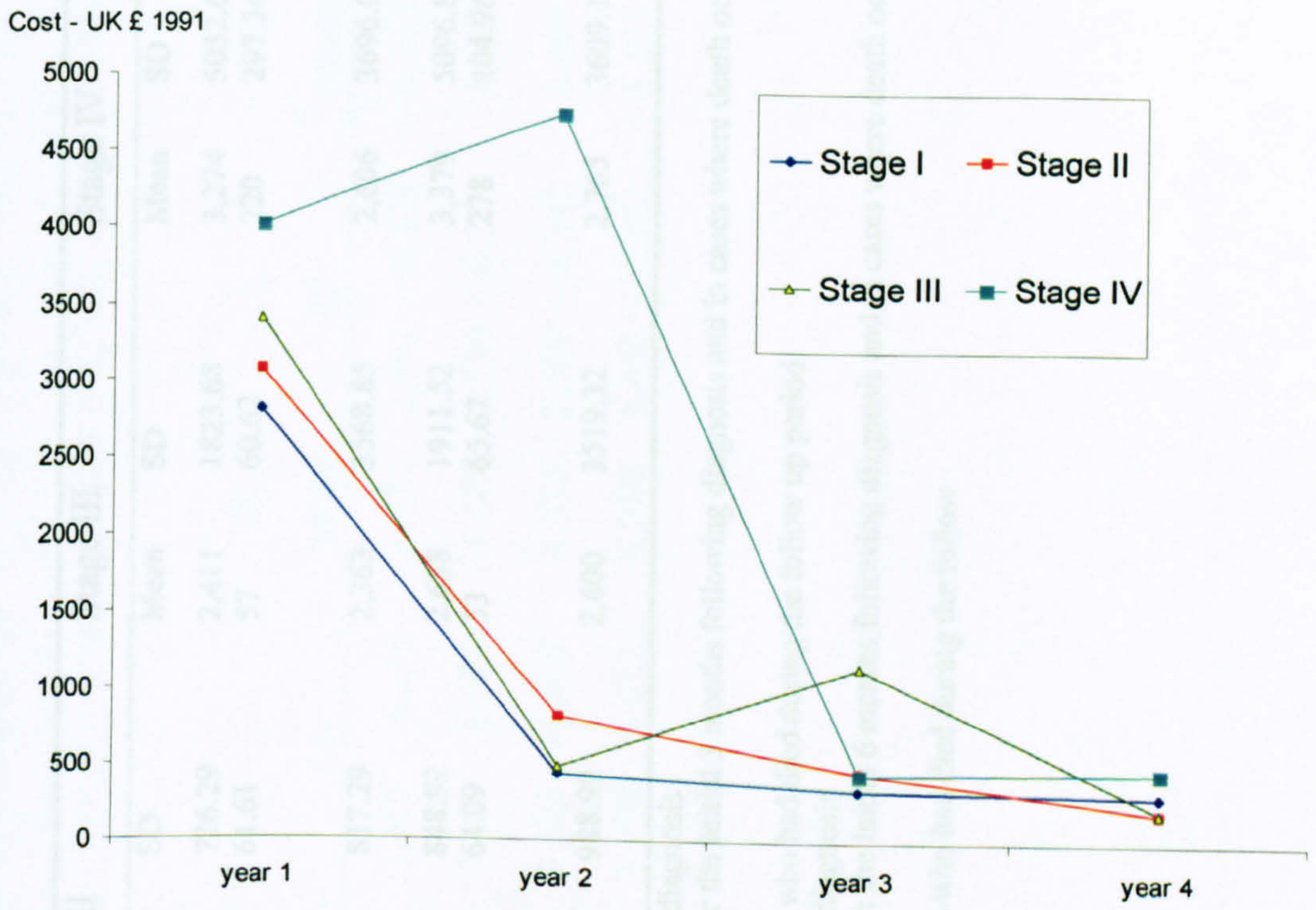


Table 5.11 Initial, continuing and terminal care costs by stage (UK £, 1991)

	All		Stage I		Stage II		Stage III		Stage IV	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Initial cost*	2,409	1899.67	2,371	1912.27	2,486	726.29	2,411	1823.68	3,274	5052.67
Continuing average monthly cost**	45	65.57	36	40.09	54	61.61	57	60.62	220	297.34
Terminal cost ***	1,694	2629.22	1,229	1773.25	867	817.29	2,363	3568.85	2,606	3696.09
Initial cost+	2,766	2080.08	2,764	2127.19	2,755	848.92	2,638	1911.52	3,379	5096.83
Continuing average monthly cost++	35	74.26	24	19.13	47	64.09	53	65.67	278	404.96
Terminal cost +++	2,016	2730.67	1,678	2195.28	1,047	988.99	2,600	3519.32	2,765	3609.16

*Initial treatment costs include all the costs initiated within the first 3 months from diagnosis

**Continuing care costs are calculated using the average monthly cost incurred after the initial 3 months following diagnosis and in cases where death occurred prior to the final 3 months of care used in estimating the terminal care costs

***Terminal care costs were calculated using the last 3 months of costs for patients who had died during the follow up period

+Initial treatment costs include all the costs initiated within the first 6 months from diagnosis

++Continuing care costs are calculated using the average monthly cost incurred after the initial 6 months following diagnosis and in cases where death occurred prior to the final 6 months of care used in estimating the terminal care costs

+++Terminal care costs were calculated using the last 6 months of costs for patients who had died during the follow

Table 5.12 Sensitivity analysis on treatment costs, by stage at diagnosis (£,1991)

		I		II		III		IV	
		Mean	CI	Mean	CI	Mean	CI	Mean	CI
Discount rate at:	6%	4,695	4,054 - 5,336	4,747	3,255 - 6,239	4,331	2,481 - 6,179	6,613	1,450 - 11,776
	0%	5,274	4,496 - 6,054	4,998	3,402 - 6,596	4,425	2,539 - 6,311	6,789	1,410 - 12,167
	3%	4,953	4,253 - 5,653	4,863	3,323 - 6,405	4,375	2,509 - 6,242	6,697	1,431 - 11,964
	9%	4,485	3,888 - 5,082	4,644	3,196 - 6,092	4,289	2,454 - 6,122	6,533	1,465 - 11,601
1-year reduced survival		4,581	3,965 - 5,196	4,666	3,188 - 6,144				

5.4 Comparison with other breast cancer costing studies (Table 5.13)

Of existing costing studies, that which appears methodologically closest to this one was conducted on a sample of 50 advanced cancer (stages III and IV) patients at Guy's Hospital, London, audited until death(33). The results of this study indicate an average diagnosis and treatment cost per patient of £7,620. The distribution of patients between the two stages was not delineated in the Guy's study and their estimate is slightly higher than the stage III and stage IV estimates (Table 5.8). Such a result might be taken to suggest a degree of consistency between the two sets of findings. This having been said, it appears that the patients in the Guy's sample were treated primarily with the prospect of cure, whilst palliation was the objective for a proportion of the Trent patients. In consequence, the treatment modalities of the two samples might have differed.

Other costing studies examining breast cancer cost by stage of the disease have found that costs increase with stage of the disease(26, 27, 35, 36).

Analyses based on models of screening programmes in Australia(37), the Netherlands(38), the USA(39) and France(40, 41) have also all concluded that treatment costs increase with disease advancement. In consequence, screening is seen to offer sizeable discounts on overall treatment costs, by facilitating the treatment of more cases at the earlier, cheaper, stages.

Without access to the other researchers' primary data it is difficult to account for the divergence between my findings and theirs, although the following are the most probable causes. First, preferred treatment modalities are likely to differ between countries: the regular use of more aggressive

interventions at the terminal illness phase, for example, would further increase the average costs of stage IV cancers. Second, the relative unit costs of resources will differ between countries, depending upon resource endowment and payment systems. The US studies(26, 39), for example, based its assessment on charges (claims through Health Maintenance Organisations) rather than costs, and the correspondence between the costs and charges is inevitably uncertain(42). A direct cost audit of an Australian hospital that examined costs over five years also concluded that costs increased with stage(43). However, the audit contained, on the authors' admission, certain biases. For example, the authors limited their analysis to the cost of treatments provided within the hospital chosen for study, with the result that certain resource usage will have been omitted. Moreover, owing to the costs and complexity of data collection, the authors assumed that treatment costs were distributed evenly over time. Given that *"the most expensive therapies - surgery with chemotherapy and/or radiotherapy - are usually provided early in the course of treatment"* then it follows that the assumption will lead to an *"underestimate of treatment costs if a positive discount rate is used"* (43:371). The assumption is accordingly likely to entail the relative underestimate of costs of early cancers, where the greatest resource use occurs early in the treatment path, and the relative overestimate of the costs of late-stage cancer costs, where the preponderance of resource use occurs later. Without this bias, in other words, it is reasonable to assume the Australian cost profile by stage would be likely to differ less from that which we have identified for the Trent sample. Indeed, it has been discovered that for breast cancer treatment and screening evaluations

generally, a perceived variation in findings between studies can typically be attributed to differences in method and measurement.

"When comparably defined programmes are evaluated using similar assumptions about consequences, very similar results are obtained" (44:117).

For the purpose of comparison with studies by Taplin *et al.* (1995)(26) and Will *et al.* (Forthcoming)(27), the costs have been split into three disease phases, initial care costs, continuing care costs and terminal care costs (see Table 5.11). Will *et al.* estimated initial care costs based on the initial 3 months of treatment costs to be between £3,022 - £4,041 (UK 1991), similar to my estimates of £2,371 - £3,274, average monthly continuing care costs are higher than the estimates for Trent; £186 compared to £44. Their estimated terminal care costs are twice that of my estimates; £5,713 compared with £1,694. Taplin *et al.* (1995) used a six-month period to estimate the costs associated, with initial, continuing and terminal care. Their estimates are approximately five times that of my estimates. However, these differences are to be expected given that their study was based in the United States and used Health Maintenance Organization (HMO) charge data. Hurley and colleagues (1992) report on the treatment costs of breast cancer recurrence in Australia. Their median cost estimate for non-fatal recurrences (inclusive of local, regional and metastatic recurrences) of £2,526 are similar to the cost estimates based on the Trent patient sample, £1,534 (1991 prices).

Table 5.13 Studies estimating breast cancer costs

Study	Country	Sample size and resource use data source	Source of unit cost data #	Currency	Price year	Stage	Cost	UK £ 91
Berkowitz *et al*, (45)	US	Incidence form NCI SEER database, care patterns from Clinical Care in America Data Warehouse	Standard Medicare payments	US $	1994	IV (metastatic)	$59,489	28,650
Butler *et al*, (35)	Australia	Medical notes of 301 patients diagnosed 1983-85, with 5 year follow up	Maintenance expenditures at the hospital – includes per diem costs and a treatment specific component	Australian $	1987/88	I II III IV	$4,289 $8,773 $11,683 $14,345	2,656 5,433 7,347 8,884
de koning *et al.* (38)	Netherlands	Medical notes of 60 patients	IP, OP and medical procedures from Dutch tariffs. Endocrine and chemotherapy - retail prices. Radiotherapy - estimated	US $	1992	Advanced	$17,100	9,142

Study	Country	Sample size and resource use data source	Source of unit cost data #	Currency	Price year	Stage	Cost	UK £ 91
Hurley *et al.* (46)	Australia	Medical notes of 128 women presenting with a breast cancer recurrence	IP/OP/DC – estimated. Investigations - clinical costing system. Drug costs -hospital pharmacy prices	Australian $ UK £	1988	Recurrence (median cost)	$4,295	2,526
						Fatal Recurrence	$10,575 $4,877	6,233
Lamarque *et al.* (40)	France	Used medical notes of 151 patients (41)	French centralized claims database	French franc	1998	I	20,483-26,611FF	1,550-2,014
						II III	38,166-44,294FF	2,889-3,353
						IV	57,809-75,646FF	4,376-5,726
							65,356-83,794FF	4,945-6,343
Legoorreta *et al.* (39)	USA	Medical records of 200 patients and 1989	HMO claims data	US $	1989	I	$23,200	13,676
						II	$28,200	16,978
						III	~$60,000	35,370
						IV	~$50,000	29,475
Richards *et al.* (33)	UK	Medical notes of 50 patients with advanced breast cancer	IP, OP, surgery, laboratory and radiology – estimated. Radiotherapy - previous study. Chemotherapy - pharmacy prices	UK £	1991	Advanced	£7,620	7,620

Study	Country	Sample size and resource use data source	Source of unit cost data #	Currency	Price year	Stage	Cost	UK £ 91
Salkeld *et al.* (37)	Australia	Treatment profiles obtained from consultation with clinical experts	Diagnosis and investigations – previous studies. IP, surgery, radiotherapy and chemotherapy - estimated	Australian $	1991	Advanced	$14,415	6,436
Taplin *et al.* (26)	USA	380,000 members of HMO, Incidence and prevalence from NCI's SEER database	HMO cost accounting system	US $	1991	Local:		
						Initial#	$10,835	6,387
						Continuing*	$8,958	5,280
						Terminal**	$14,962	8,820
						Regional:		
						Initial*	$12,273	7,235
						Continuing*	$1,423	839
						Terminal***	$20,323	11,980
						Distant:		
						Initial*	-	-
						Continuing**	$2,921	1,722
						Terminal***	$20,610	12,150

Study	Country	Sample size and resource use data source	Source of unit cost data #	Currency	Price year	Stage	Cost	UK £ 91
Will *et al.* (36)	Canada	Incidence from Canadian Cancer Registry, practice patterns and stage distribution from survey of oncologists, surgeons and radiotherapists Length of stay and numbers associated with care paths from Statistics Canada and medical notes.	Per diem rates – Ontario care cost project. Drug costs and administration, radiotherapy – Ottawa Regional Cancer Center Study. OP – previous studies. Tamoxifen – pharmacy prices	Canadian $	1995	First 3 months of diagnosis and therapy I II III	 $8,014 - 8,225 $8,048 – 10,140 $8,073 - 8,315	 2,948 – 3,026 2,961 – 3,730 2,970 – 3,059
Will *et al.* (27)	Canada	Review of 600 medical notes	Manitoba Health charges and Ontario care cost project.	Canadian $	1995	Lifetime cost estimates I II III IV	$23,275 $25,658 $32,197 $36,340	8,563 9,439 11,845 13,369

The term ***estimated*** means that costs were estimated using a bottom up costing approach using information on staff workload, salaries, capital, consumables, overheads etc.
* initial care costs = first six months' costs
** continuing care costs = 3 months of continuing care costs
*** terminal care costs = last six months' costs

5.5 The Effect of Screening

5.5.1 Background

Whilst the effectiveness of breast cancer screening appears beyond dispute, discussion continues over the extent to which effectiveness translates into cost-effectiveness. The evaluation that supported the introduction of mass screening into the United Kingdom - the Forrest Report(47) - produced a minimum estimate of cost per life-year gained of approximately £3,000 at 1984 prices. Although the Forrest estimates, revised for inflation, appear to have subsequently occupied a permanent place in the "cost-effectiveness league table", it is important to appreciate that they have been the subject of criticism, especially with respect to the quality of data employed(48-50). For example, given that mass screening had yet to be implemented at the time of the evaluation, the values of many of the parameters within the overall cost-effectiveness calculations, such as the unit cost of screening, compliance and rates of recall, had to be modelled from trial data. Whilst the use of such methods was by no means illegitimate at the time of the original evaluation, the fact that the UK screening programme has now been in operation for some time means that we currently possess realistic data for these parameters.

At the time of the Forrest evaluation, no attempt was made to estimate possible changes in overall cancer treatment costs occasioned by the introduction of screening. Were they to exist, however, differential treatment costs between a screened and non-screened population would represent a point of substance. If early-stage cancers are actually cheaper to treat than cancers at later stages, the screening programme could be

expected to produce economies in direct health care costs in addition to the survival benefits accruing to patients. On the other hand, if the treatment of late-stage disease proves to be the cheaper, then the cost-effectiveness estimates suggested by the original evaluation were over-optimistic. Stage specific cost estimates have been used in a number of studies evaluating the cost-effectiveness of breast cancer screening(37-40), and have suggested that the former possibility is the more likely. However, resolution of this issue in the UK context requires an estimate of the diagnosis, treatment and follow-up costs of breast cancer by stage.

5.5.2 Methods

Based on these models of evaluation(37-40), I decided to incorporate the treatment cost information into a comparison of the costs and outcomes of the screening programme in the Trent region with that of a hypothetical scenario, one that assumes that screening had not been introduced and that all cancers had been detected in other ways. For consistency, I have attempted to follow an approach similar to that employed in the original Forrest evaluation(47). The analysis requires the following data and assumptions.

The UK screening programme was introduced gradually between 1987 and 1990. Trent Cancer Registry data indicate that the annual registration rate of new cases of breast cancer prior to the introduction of screening was roughly constant: the registration rates for 1986 through 1988 were 969, 974 and 962 per million women, respectively. As would be expected, the introduction of screening very quickly raised this rate to 1,147 in 1992, although the rate thereafter fell to 956 per million in 1994.

It therefore appears reasonable to assume that the sensitivity of, and compliance with, mammography have been sufficiently high for the earliest screening rounds to have been successful in identifying the preponderance of prevalent cancers. In the future, therefore, incidence screens will be detecting essentially the same number of cancers as that resulting from symptomatic presentation prior to screening. I have therefore assumed that the effect of incidence screening is to improve the staging distribution at diagnosis, with no effect on cancer yield.

5.6 Using the cost and staging data to inform the cost-effectiveness of breast cancer screening

In the Trent region and in the reference year (1991), 106,172 women were invited for screening, 81,694 attended and 5,825 were recalled for further investigation(51). The unit costs of screening this cohort were assumed to be the average cost of mammography as employed in the earlier unit cost estimates (£22). The assessment of suspected cancers following recall varied with both condition and practitioner and I employed average figures based on stage-specific mean costs derived from the cost audit of screened patients in Trent. The costs were £49, £37, £22 and £22 for stages 1 through 4, respectively, yielding a weighted average of £47.

The Forrest evaluation was conducted prior to the introduction of mass screening, with the result that programme administration costs were not included in that cost per life-year estimate. Administration of the programme, however, is a current reality although no formal accounts

appear to be available. I have employed an estimate of £7 per woman invited, provided by the Nottingham screening unit(52).

In 1991, there were 2,687 new breast cancer registrations in the Trent region. Of the cancers in the Trent sample, 32 per cent had been detected as a result of screening, 46 per cent were self-detected, whilst the remainder were discovered primarily through examinations by general practitioners. The distribution of cancers by stage was 74, 10, 12 and 4 per cent for stages I through IV, respectively. For the screening scenario, I assumed that the 2,687 cancers presented or were detected according to this stage distribution. For the no-screening scenario, I assumed that these cancers would have presented according to the staging distribution of the sub-sample of those cancers <u>not</u> detected by screening. This was 68, 11, 16 and 5 per cent for stages I through IV, respectively. As expected, this latter distribution was comparatively inferior from the prognostic point of view.

As a measure of life-year gains by stage in both scenarios, I used the sample survival data described earlier. Although there exists a debate over whether and how survival gains should be discounted in economic evaluations(53-55), I have discounted life-year gains at the same rate as for costs, to ensure consistency with the Forrest methodology. In summary, therefore, the approach was to estimate the cost and survival impact of a screening programme whose sole effect would be to improve the staging distribution at diagnosis. Appendix 5.6 summarises these assumptions used in the screening model.

5.7 Results from the screening model - Cost-effectiveness of screening

The results of comparing the screening scenario with the no-screening scenario appear in Table 5.14. As may be seen, the shift in stage distribution occasioned by screening entails higher total treatment costs for stage I cancers, although these are almost completely offset by lower treatment costs for cancers at stages II through IV. Overall, the diagnosis, treatment and follow-up costs of screened patients are higher than those under the no-screening scenario, although by only 0.5 per cent.

Table 5.15 presents the results of a sensitivity analysis, allowing for variations in treatment costs by stage within the estimated confidence intervals and changes in the discount rate. I have also relaxed the assumption that early-stage cancers incur additional treatment costs beyond the fourth year, i.e. such patients are deemed to return to the "normal" population. As may be seen, lower discount rates contribute significantly to improving the cost-effectiveness ratio. The effect of reduced life expectancy for early-stage cancer is also investigated.

In the model, the change in the distribution of cancer stages occasioned by screening was inferred from data collected at a particular point in time, whilst a screening programme was actually in progress. However, studies conducted in Southampton, UK(13), and in Texas, USA(56), have reported on the staging distributions actually observed both before and after the introduction of mass screening programmes. Their observed distributional changes are at variance with those inferred from our Trent data in one important respect. The observational studies both suggest that screening

increases the proportion of cancers detected at early stages (I and II combined) by around 5 percentage points, a figure only marginally lower than my assumed increase of around 7 points. However, the findings of both studies suggest that the assumption of 68 per cent of cancers in an unscreened population being detected at stage I may be unrealistic or atypical. Each reports a proportion of unscreened stage I detections of around a much lower 23 per cent, with a correspondingly higher proportion of stage IIs (55-60 per cent). Screening then shifts the distribution, such that stage I detection rises to 45-50 per cent of the total, with stage II detection falling to 30-40 per cent.

Re-estimating the model, using the Southampton and Texas pre- and post-screening distributions in place of our assumed Trent distributions, produces broadly similar estimates of the treatment cost increase occasioned by screening, namely, 0.3 and 0.5 per cent, respectively. Whilst the changes in the stage distribution assumptions have no impact on the costs of the screening programme, expected survival gains increase considerably relative to the base-line estimate. This is due to the large rise in stage I detections, where potential life gains are the highest, being only partially offset by the losses from a smaller proportion of stage II detections. In consequence, the estimate of the cost per life-year gained from screening falls to £1,636 and £1,244 for the Southampton and Texas stage distributions, respectively. These figures represent a fall of 51 and 63 per cent, respectively, from the base estimate. Impressive as they are, however, the previously noted caveat relating to the known variability of staging by study site should be borne in mind(32).

Although the Forrest Working Group produced estimates of the time and travel costs of screening these do not appear to have been included in the final cost per life-year calculation. However, using more recent estimates of time and travel costs(57), it is now possible to include such factors. Revised to 1991 values, the mean costs per visit were £1.7 for travel and £5.0 for time, these amounts were added to each element of activity where such costs might be expected to be incurred, e.g. attendance for screening, in-patient and out-patient visits and follow-up[5.3]. The inclusion of such time and travel costs increases the estimated expected lifetime treatments costs by 5.3, 5.2, 3.9 and 1.7 per cent for cancers at stages I to IV, respectively. The expected gross (health service plus time and travel) cost of implementing the screening programme as originally modelled rises from around £2.8 million to around £3.4 million, an increase of around 21 per cent. In consequence, the estimate of cost per life-year gained from screening rises to £4,086.

[5.3] It should be borne in mind that of course these costs are going to under represent the time costs involved in inpatient stays.

Table 5.14 Cost-effectiveness of screening in Trent (£, 1991)

			No screening [1]	Screening [2]	[2]-[1]
Treatment costs by stage (£):		1	8,578,516	9,335,444	756,928
		2	1,403,071	1,275,519	-127,552
		3	1,861,984	1,396,488	-465,496
		4	888,457	710,765	-177,691
	TOTAL		12,732,027	12,718,216	-13,811
Cost of screening programme (£):	Invitation			747,818	
	Mammography			1,802,170	
	Recall investigations			273,109	
	TOTAL			2,823,097	
Total costs (£):			12,732,027	15,541,313	2,809,286
Expected life years by stage:		1	14,090	15,333	1,243
		2	1,742	1,584	-158
		3	799	600	-200
		4	250	200	-50
	TOTAL		16,881	17,716	835
Cost per life year gained by screening (£):					3,364

Table 5.15 Sensitivity analysis of cost-effectiveness results for breast cancer screening

		Cost per life-year (£,1991)	Change from baseline (%)
Baseline		3,364	
Lower CI of base costs		3,692	10
Upper CI of base costs		3,036	-10
4-year costs only		3,190	-5
Discount rate:	0%	2,315	-31
	3%	2,802	-17
	9%	4,007	19
1 year reduced survival (stage 1 & 2)		3,647	8
Stage distributions	(Moody *et al*)	1,636	-51
	(Roberston *et al*)	1,244	-63
Time and travel costs included		4,086	22

5.8 Breast cancer screening – comparisons with other studies

Tables 5.16 and 5.17 display the results from cost-effectiveness and cost-utility analyses of breast cancer screening. They differ in respect to the country of evaluation, screening intervention, screen interval and target age group. They also differ in respect to how the analyses were conducted, some are directly based on data from pilot studies or actual screening programmes(21, 58-61), while others(47, 62-68) are secondary analyses of previous case-control studies and trials, such as the Nijmegan study(69), the Health Insurance Plan Study(70), the Swedish two-counties study(71), the Malmo trial(72, 73), and the Utrecht study(74). However, the results, for those with a similar intervention; mammography, screen interval; biennial, and target age group; 50-64 years, are comparable with the Trent data results. The results range from £3,135 to £4,994 (£, UK 1991)(47, 62, 63, 75). The results for those studies that evaluated biennial breast cancer screening by mammography for the 50-69 age group display greater variation, £2,769-£9,573(59-61, 65-67, 75).

Table 5.16 Review of Cost-Effectiveness Analyses of Breast Cancer Screening*

Country	Study	Screen Strategy #	Screen Interval	Age group	Source of effectiveness	Follow up period	Discount rate	Currency/ Year	Cost per life year saved (original)	Cost per LYS UK £ 1991**
UK	Gravelle et al 1980(21)	BPE + MG	Not stated	40+	Ravenor Park Screening unit, Middlesex	4 years 1973-77	costs @ 5%	£ UK 1980	£832-1,359	£1,622-2,650
UK	Forrest 1986(47)	MG	3 yearly	50-64	HIP(70, 76)& 2 Counties(71)	15 years	costs @ 5%	£ UK 1983-84	£3,044	£4,688
UK	Knox 1988(62)	MG	3 yearly	50-64	HIP(70, 76) & 2 Counties(71)	not stated	not stated	£ UK 1988	£2,591	£3,135
Spain	Garuz et al 1997 (63)	MG	Biennial	50-65	Decision analysis and markov model based on various published sources(72, 73)	Markov model based on 15 cycles (no indication of what these cycles were)	Costs @ 6%	ECU 1993	7,300 ECU	£4,834
				45-49					9,400 ECU	£6,225
Spain	Plans et al. 1996 (64)	BPE + MG	Not stated	50-64	Synthesis of previous studies	Not stated	Not stated	$ US 1990	$8,424 (per cancer detected)	£5,617 (per cancer detected)

Country	Study	Screen Strategy #	Screen Interval	Age group	Source of effectiveness	Follow up period	Discount rate	Currency/ Year	Cost per life year saved (original)		Cost per LYS UK £ 1991**	
Japan	Okubo et al. 1991(77)	MG &/or BPE	Annual	30+	Literature, and Japanese government statistics	50 years	costs @ 5%	$ US date not stated (assumed 1990)				
		BPE alone	Annual	30+					$49,700		£33,138	
		MG	Annual	30+					$14,300		£9,535	
		BPE →MG	Annual	30+					$40,400		£26,937	
		BPE + MG	Annual	30+					$18,200		£12,135	
Australia	Hall et al. 1992(58)	MG	Biennial	45-69	Pilot programme in Western Sydney	1 year	costs @ 5%	$ AUS 1988/89	$7190		£3,889	
Australia	Carter et al. 1993(65)	MG	2-3 yearly	40-69	Malmo(72),	30 years	costs @ 5%	$ AUS 1990		ICER		ICER
			Biennial	50-69	2 counties(71),				$14,733	$22,093	£7,096	£10,641
			3 yearly	50-69	Nijmegan(69),				$13,081	Baseline	£6,276	Baseline
			Annual + Biennial	40-49 + 50-69	Utrecht(74)				$27,527	$54,237	£13,077	£26,123
			Biennial + 3 yearly	40-49 + 50-69					$19,919	$49,029	£9,557	£23,614
			Biennial	40-69 + 50-69					$20,300	$35,952	£9,739	£17,316

Country	Study	Screen Strategy #	Screen Interval	Age group	Source of effectiveness	Follow up period	Discount rate	Currency/ Year	Cost per life year saved (original)	Cost per LYS UK £ 1991**
Netherlands	van der Maas et al. 1989(66)	MG	1-4 yearly	50-70	HIP(70, 76), 2 counties(71), Nijmegan(69), Utrecht(74)	27 years 1988-2015	costs and effects @ 5%	$ US 1988		
									ICER	ICER
			4 yearly	52-68					$4,050 Baseline	£2,932 Baseline
			Biennial	51-69					$6,050 $6,050	£4,380 £4,380
			16 months	50-69					$12,900 $12,900	£9,338 £9,339
			Annual	50-69					$14,800 $14,800	£10,713 £10,715
Netherlands	de Koning et al. 1991(67)	MG	Biennial	40-70	Nijmegan(69), Utrecht(74)	Simulation of 27 years 1990-2017	costs & effects @ 5%	$ US 1988	$5,400	£3,909
				50-70					$3,825	£2,769
Netherlands	Van Inveld et al 1993 (78)	MG	Biennial	50-70	Country specific data on incidence, mortality, demography, screening organisation and price levels	Simulation of 27 years 1990-2017	costs & effects @ 5%	£ UK 1990	£2,120	£2,304
Spain									£9,700	£10,544
France									£5,800	£6,305
UK									£1,800	£1,957

Country	Study	Screen Strategy #	Screen Interval	Age group	Source of effectiveness	Follow up period	Discount rate	Currency/ Year	Cost per life year saved (original)	Cost per LYS UK £ 1991**
Norway	Norum 1999 (61)	MG	Biennial	50-69	Norwegian mammography screening project	Not stated	costs & effects @ 5%	£ UK (date not stated – assumed 99)	£8,561	£6,309
Finland	Leivo et al. 1999 (60)	MG	Biennial	50-59	Finnish breast screening programme(79)	5 years for costs 1987-1992 estimated LY 1987-2020	costs & effects @ 3%	$ US 1995	$18,955	£9,573
Germany	Beemsterboer et al (1994)(59)	MG	Biennial	50-69	2 pilot regions in Germany and Swedish trial(73)	Modelled for 27 years	costs @ 5% effects no discount	German DM 1994	DM 18,800	£5,977
New Zealand	Szeto et al. 1996 (75)	MG	Biennial	50-64	Model based on authors assumptions	Costs based on all breast cancers during 1993-94 estimated LY 1996-2025	costs & effects @ 5%	$ NZ 1991	ICER $14,510 $22,264 $12,668 Baseline $14,597 $18,530 $15,169 $19,102	ICER £4,994 £7,663 £4,360 Baseline £5,024 £6,378 £5,221 £6,574
			3	50-64						
			Biennial	50-69						
			Biennial	45-64						

Country	Study	Screen Strategy #	Screen Interval	Age group	Source of effectiveness	Follow up period	Discount rate	Currency/ Year	Cost per life year saved (original)	Cost per LYS UK £ 1991**
USA	Rosenquist and Lindfors 1994 (80)	MG	Annual	40-85 40-49 40-49	Markov model assuming 30% reduction in mortality	Not stated	No discounting costs & effects @ 5%	$ US (year not stated)	$18,600 $26,200 $46,300	£10,293 £14,498 £25,621
USA	Eddy et al. 1989(68)	BPE &/or MG	Annual	40-75	BCDDP(81) & HIP(70, 76)	11 years 1989-2000	costs & effects @ 5%	$ US 1989	BCDDP/ HIP $1,409 / $33,000 $29,427 / $134,081	BCDDP/ HIP £10,042 / £22,841 £20,368 / £92,804
		BPE		40-50					$8,113 / $15,536	£5,615 / £10,753
		BPE+MG		55-65					$21,717 / $83,830	£15,031 / £58,023
		BPE		65-75					$9,597 / $17,175	£6,643 / £11,886
		BPE+MG		65-75					$25,395 / $92,412	£17,577 / £63,936

* All studies used a no screening policy as a comparator, except Eddy et al. (1989) who identified the cost-effectiveness of mammography when added to the existing programme of breast examination.
# BPE = breast physical examination, MG = mammography
** Conversion to UK prices using exchange rates and HCHS pay and price index to adjust to 1991 prices(82)

Table 5.17 Review of Cost-Utility Analyses of Breast Cancer Screening.

Country	Study	Currency/Year	Age group	Cost per QALY/HYE (original)	Cost per QALY/HYE (UK £ 1991)
UK	Forrest 1986(47)	£ UK 1983/84	50-64 years	£3,309	£5,096 per QALY
Germany	Beemsterboer *et al.* (1994)(59)	German DM 1994	50-69 years	DM 19,800	£6,295 per QALY
Netherlands	de Koning *et al.* 1991(67)	$ US 1988	40-70 years	$35,000	£26,892 per QALY
			50-70 years	$4,050	£3,112 per QALY
Australia	Hall *et al.* 1992(58)	$ AUS 1988/89	45-69 years	$16,355	£11,943 per HYE

5.9 Conclusions

As a result of a detailed, patient-specific resource audit, the conclusion is that screening is unlikely to offer the prospect of significant treatment cost economies. Although late-stage patients consume relatively large amounts of palliation resources, their high costs are counter-balanced by early-stage patients consuming more surgical and follow-up resources. It is interesting to note that these reservations about the potential for treatment cost reduction by screening are shared by the authors of a systematic review of the literature, who conclude that the assumption of a wide differential between lifetime treatment costs for early- and late-stage cancer "*is almost surely fallacious*"(44:115).

This having been said, there appear grounds for believing that the original Forrest estimate may have under-stated the cost-effectiveness of breast cancer screening in the UK. Translated into 1991 values, the basic cost per life-year estimate from the Forrest Report becomes approximately £4,500. Employing a Forrest-type cost-effectiveness methodology with the Trent data, we have obtained a base-line figure some 25 per cent lower. This figure, it should be recalled, includes invitation costs. Experiments with other observed changes in staging distributions suggest that even this base-line figure might be an over-estimate, whilst the inclusion of private costs still yields a base-line cost-effectiveness ratio superior to the original Forrest estimate without private costs.

It is perhaps necessary to make explicit that the intention of the latter part of the analysis has been to enhance the understanding of the technical efficiency of breast cancer screening. The fact that an intervention's cost-effectiveness ratio might be more favourable than had originally been thought does not, of course, mean that the intervention is necessarily worthwhile per se.

Moreover, in reaching decisions about the management of screening programmes, "*...technical efficiency is simply one argument in a complex function which also includes ethical, medico-legal, and emotional considerations.*" (83:31).

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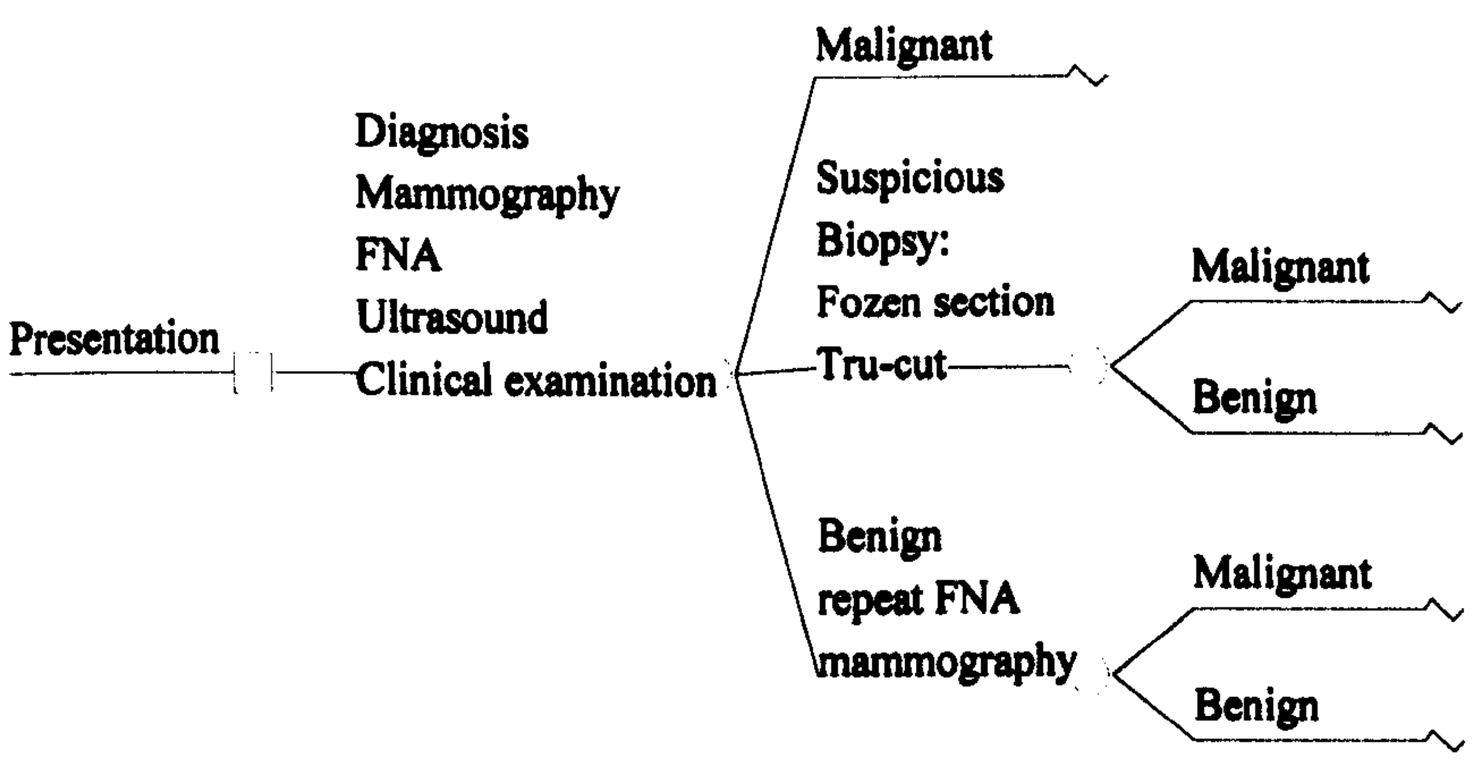
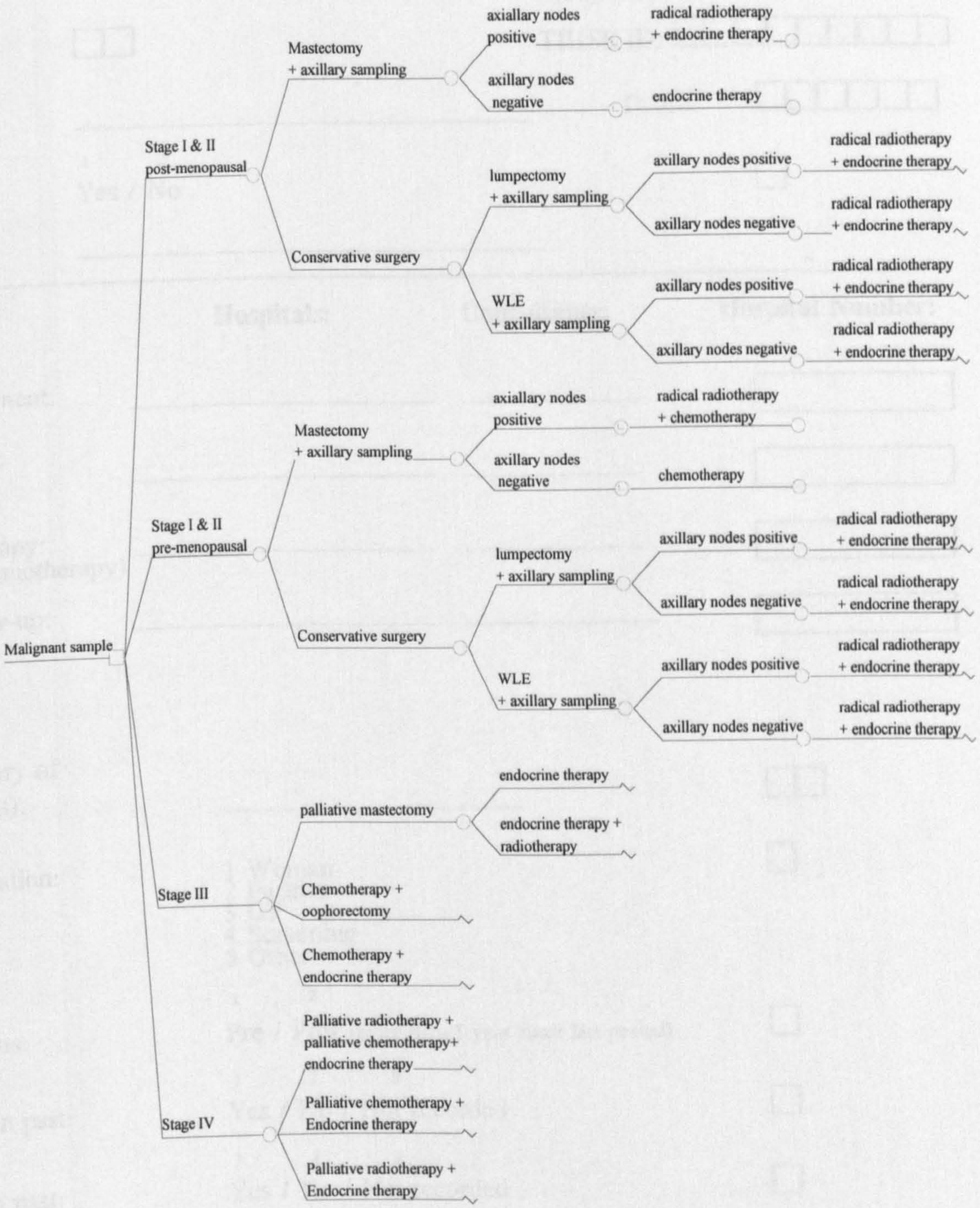
Appendix 5.1 Diagnosis/staging algorithm for breast cancer from the literature



Treatment algorithm for breast cancer by stage from the literature.



CANCER IN TRENT
Breast Cancer Abstract
DIAGNOSIS FORM

Abstracter: ☐☐

Appendix 5.2

BASIC INFO

Current Date: ☐☐☐☐☐☐

Study No: ☐☐☐

District Code: ☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

Patient's Name: _____ D.o.b. ☐☐☐☐☐☐

1 2

Clinical Trial: Yes / No ☐

Trial Number: _____

Treatment	**Hospitals:**	**Consultants:**	**Hospital Number:**
1) Primary Treatment: (ie.surgery)	_____	_____	☐
2) Radiotherapy:	_____	_____	☐
3) Systemic Therapy: (Hormone/Chemotherapy)	_____	_____	☐
4) Regular follow-up:	_____	_____	☐

HISTORY

Duration of history of **symptoms** (weeks): _____ ☐☐

Mode of presentation: ☐

1 Woman
2 Partner
3 GP
4 Screening
5 Other

1 2

Menopausal status: Pre / Post (more than 1 year since last period) ☐

1 2 9

Oophorectomy in past: Yes / No / Not recorded ☐

1 2 9

Hysterectomy in past: Yes / No / Not recorded ☐

CANCER IN TRENT
Breast Cancer Abstract

DIAGNOSIS FORM

Abstracter: ☐☐☐

DIAGNOSIS

Mode of first diagnosis: ☐

1 FNA
2 Core biopsy
3 Operation
4 Other _____

Date of first diagnosis: (IP/DC/OP) ☐☐☐☐☐☐

Date admitted ☐☐☐☐☐☐

Date discharged ☐☐☐☐☐☐

DIAGNOSIS (continued)

Further diagnosis: 1 Yes / 2 No ☐

Date: (IP/DC/OP) ☐☐☐☐☐☐

Date admitted ☐☐☐☐☐☐

Date discharged ☐☐☐☐☐☐

Mode: ☐

1 FNA
2 Core biopsy
3 Operation
4 Other _____

Clinical staging at primary diagnosis
TNM as recorded in notes T ☐ N ☐ M ☐

TREATMENT OF PRIMARY

Surgical treatment of primary: 1 Yes / 2 No ☐

Date of first surgery: (d/m/y) ☐☐☐☐☐☐

IP/DC/OP _____

Date admitted ☐☐☐☐☐☐

Date discharged ☐☐☐☐☐☐

Type of surgery:

1 Breast procedure: ☐

1 None
2 Incision biopsy
3 Excision biopsy/lumpectomy
4 Wide local excision
5 Segmentectomy/quadrantectomy
6 Subcutaneous mastectomy
(No skin removed.
Nipple preserved.)
7 Simple mastectomy/total mastectomy
(No muscle removed)
8 Modified radical mastectomy
9 Radical mastectomy

CANCER IN TRENT
Breast Cancer Abstract
DIAGNOSIS FORM

Abstracter: ☐☐

SURGERY (continued)

2 Axillary procedure:

1 None
2 Sampling
3 Clearance

☐

Second surgical procedure:

1 2
Yes / No

☐

Date: (d/m/y) ☐☐☐☐☐☐

IP/DC/OP _____

Date admitted ☐☐☐☐☐☐

Date discharged ☐☐☐☐☐☐

Type of surgery: BP _____ ☐

AP _____ ☐

Radiotherapy: ☐

1 Not given
2 Breast/chest wall
3 Axilla/gland fields
4 Combined (eg breast & axilla)
9 Not specified

Date started: (d/m/y) ☐☐☐☐☐☐

Date finished: (d/m/y) ☐☐☐☐☐☐

IP/OP/DC _____

ADJUVANT SYSTEMIC THERAPY ☐

1 None
2 Chemotherapy
3 Endocrine therapy
4 CT & ET
9 Not specified

1 Chemotherapy

1 CMF ☐
2 Others -
specify _____

Date started: ☐☐☐☐☐☐

Date finished: ☐☐☐☐☐☐

IP/OP/DC _____

2 Endocrine therapy

Drugs: ☐

1 Tamoxifen
2 Aminoglutethimide
3 Other _____

Date started: ☐☐☐☐☐☐

Date finished: ☐☐☐☐☐☐

IP/OP/DC _____

CANCER IN TRENT
Breast Cancer Abstract
DIAGNOSIS FORM

Abstracter: ☐☐☐

TREATMENT (continued)

Oophorectomy: 1 Yes / 2 No ☐

Date started: ☐☐☐☐☐☐

Date finished: ☐☐☐☐☐☐

IP/OP/DC _____

Palliative care 1 Yes / 2 No ☐

Date started: ☐☐☐☐☐☐

Date finished: ☐☐☐☐☐☐

IP/OP/DC _____

FOLLOW UP/OUTCOME

Local recurrence, distant metastases, vital status

Local recurrence: (Breast/chest wall) 1 Yes / 2 No ☐

Date of first local recurrence: (d/m/y) ☐☐☐☐☐☐

Regional recurrence: (Axilla/SCF) 1 Yes / 2 No ☐

Date of first regional recurrence: (d/m/y) ☐☐☐☐☐☐

Contralateral breast recurrence: 1 Yes / 2 No ☐

Date of first contralateral breast recurrence: (d/m/y) ☐☐☐☐☐☐

Distant metastasis: 1 Yes / 2 No ☐

Date of first distant metastasis: (d/m/y) ☐☐☐☐☐☐

Site of first distant metastasis: ☐

1 Liver
2 Lung
3 CNS
4 Bone
5 Pleura effusion
6 Ascites
7 Other - specify _____

CANCER IN TRENT
Breast Cancer Abstract
DIAGNOSIS FORM

Abstracter: ☐☐☐

Frequency of Investigations Per Year

Investigation	1991	1992	1993	1994	1995	comment
Outpatient check up						
Radiotherapy clinic check up						
Clinical examination						
Mammogram						
FNA						
Chest X-ray						
Ultrasound						
Other:						
Other:						

1 2

Vital status: Dead / Alive ☐

Date of death/date last seen: (d/m/y) ☐☐☐☐☐☐

COMMENTS:

CANCER IN TRENT
Breast Cancer Abstract

DIAGNOSIS FORM Abstracter: ☐☐☐

CLINICAL TNM STAGING

SKIN - BREAST AREA ONLY

(T1) 1 Normal
(T2) 2 Incomplete fixation (tethered or dimpled)
(T3) 3 Complete fixation within tumour area (infiltrated or ulcerated)
(T3) 4 Peau d'orange within tumour area
(T4) 5 Peau d'orange or skin involvement wide of tumour area (but not wide of breast)

NIPPLE

1 Normal
(T2) 2 Retracted
3 Paget's disease (confined to nipple)
(T2) 4 Paget's disease (wide of nipple)

PECTORAL MUSCLE	(T2)	1 No fixation
	(T3)	2 Fixed
CHEST WALL	(T2/T3)	1 No fixation
	(T4)	2 Fixed
AXILLARY LYMPH NODES (same side)	(N0)	1 None palpable
	(N1)	2 Palpable and mobile
	(N2)	3 Palpable and fixed
	(N3)	4 Oedema of arm
SUPRACLAVICULAR and **INFRACLAVICULAR** NODES (same side)	(N0)	1 None palpable
	(N3)	2 Palpable
OTHER METASTASES (including skin wide of breast other breast contralateral lymph nodes, etc)	(M0)	1 None found
	(M1)	2 Present

T ☐ N ☐ M ☐ Stage I II III IV ☐

Appendix 5.3 Estimating life expectancy

Linear trend

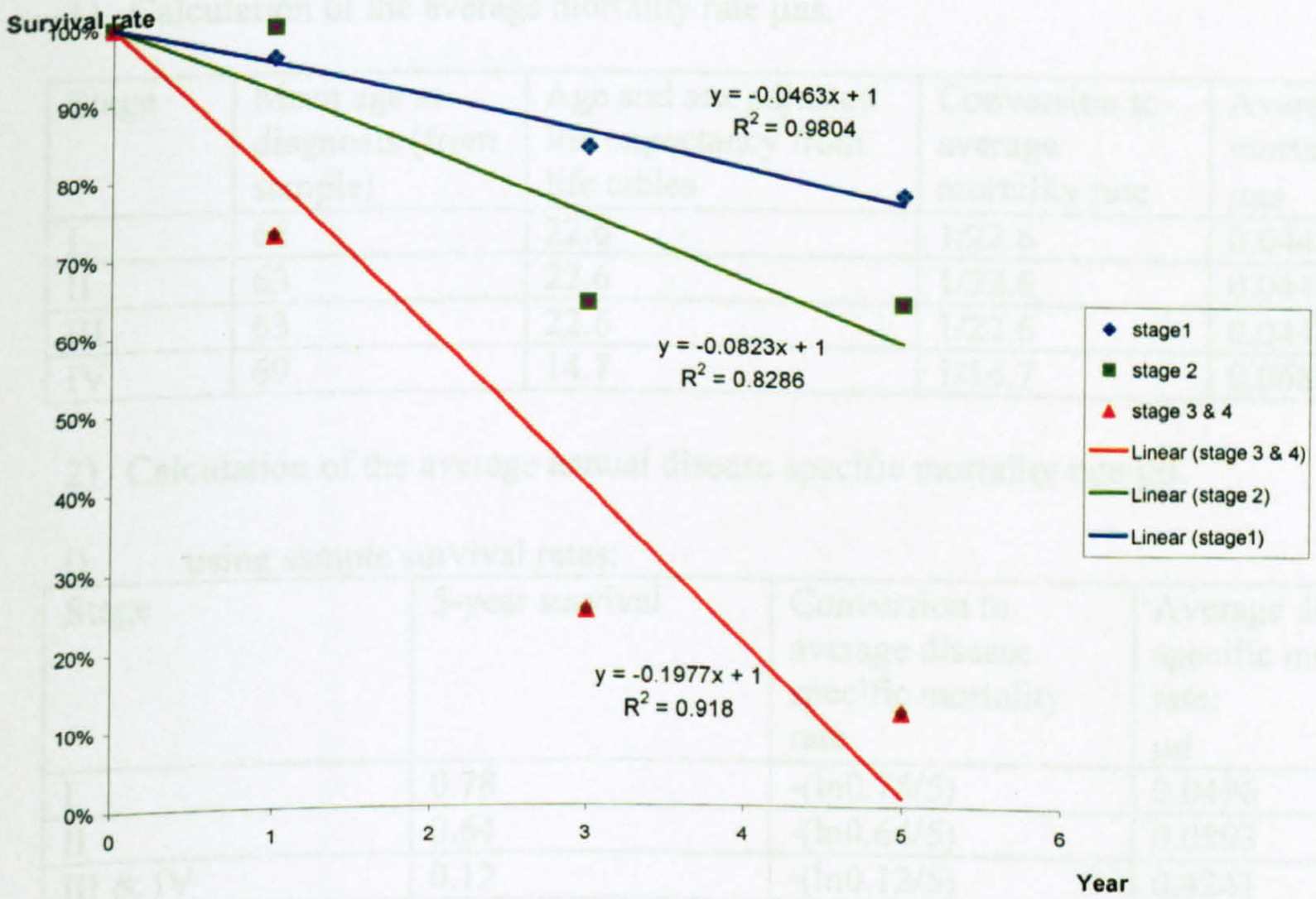
Sample survival rates by stage

	Year 0	Year 1	Year 3	Year 5
Stage I	1.00	0.96	0.84	0.78
Stage II	1.00	1.00	0.64	0.64
Stage III & IV	1.00	0.73	0.25	0.12

Trends for sample survival rates

Survival estimates are obtained using information from the stage specific linear trend-lines:

Stage I = (1/0.0463)/2 =10.79 years
Stage II = (1/0.0823)/2 = 6.07 years
Stage III = (1/0.977)/2 = 2.53 years



DEALE method

1) Take the reciprocal of the age-sex-adjusted life expectancy to obtain the age-sex-adjusted average mortality rate μas.
2) Obtain the disease specific mortality rates. For this single point survival data (e.g. 5-year, 10-year) can be used. They are converted into mortality rates by logarithmic transformation. The average annual rate can be calculated using the following equation:

$$\mu d = -\frac{1}{t}\ln(S)$$

Where t = time
S = survival proabaility
e.g. if 5-year survival rate = 0.81 t = 5 and s = 0.81

3) Take the recipricol of the sum of μas and μd to obtain the life expectancy.

1) Calculation of the average mortality rate μas.

Stage	Mean age at diagnosis (from sample)	Age and sex adjusted life expectancy from life tables	Conversion to average mortality rate	Average mortality rate: μas
I	61	22.6	1/22.6	0.04425
II	63	22.6	1/22.6	0.04425
III	63	22.6	1/22.6	0.04425
IV	69	14.7	1/14.7	0.06803

2) Calculation of the average annual disease specific mortality rate μd.

i) using sample survival rates:

Stage	5-year survival	Conversion to average disease specific mortality rate	Average disease specific mortality rate: μd
I	0.78	-(ln0.78/5)	0.0496
II	0.64	-(ln0.64/5)	0.0893
III & IV	0.12	-(ln0.12/5)	0.4241

ii) using Cancer Research Campaign reported survival rates[Cancer Research Campaign, 1991 #1065]:

Stage	5-year survival	Conversion to average disease specific mortality rate	Average disease specific mortality rate: μd
I	0.84	-(ln0.84/5)	0.0348
II	0.71	-(ln0.71/5)	0.06
III	0.48	-(ln0.48/5)	0.15
IV	0.18	-(ln0.18/5)	0.34

3) Take the recipricol of the sum of μas and μd to obtain the life expectancy:

i) for sample stage survival data:

Stage	Converion to life expectancy	Life expectancy (years)
I	1/(0.04425+0.0496)	10.66
II	1/(0.04425+0.0893)	7.49
III & IV	1/(0.06803+0.4241)	2.03

ii) for CRC survival data:

Stage	Converion to life expectancy	Life expectancy (years)
I	1/(0.04425+0.0348)	12.65
II	1/(0.04425+0.06)	9.59
III	1/(0.04425+0.15)	5.15
IV	1/(0.06803+0.34)	2.45

Appendix 5.4 Total Resource Use by Stage - Breast cancer

	Stage I (n=102)	Stage II (n=13)	Stage III (n=16)	Stage IV (n=6)
Mode of Presentation				
Self	43 (43%)	8 (62%)	8 (53%)	2 (33%)
partner	1 (1%)	-	-	
GP	14 (14%)	1 (85%)	4 (27%)	1 (17%)
screen	37 (37%)	3 (23%)	1 (7%)	1 (17%)
other	5 (5%)	1 (8%)	2 (13%)	2 (33%)
Screening				
mammography	15 (15%)	2 (15%)	1 (6%)	1 (17%)
mammography/tru-cut biopsy	2 (2%)			
mammography/fna	13 (13%)	1 (8%)		
mammography/fna/ Ultrasound	7 (7%)			
Diagnosis				
Primary diagnosis	89 (87%)	12 (92%)	16 (100%)	6 (100%)
mammography	11 (11%)	1 (7%)	2 (13%)	
Tru-cut biopsy	16 (16%)	2 (13%)	3 (19%)	1 (17%)
Fna	35 (34%)	4 (31%)	8 (50%)	2 (33%)
ultrasound	2 (2%)			
mammography/fna	9 (9%)			
fna/tru-cut biopsy	2 (2%)			
mammography/fna/ ultrasound		1 (7%)		
Frozen section biopsy	2 (2%)	1 (7%)		
Marker biopsy	10 (9%)	1 (7%)		
Physical examination	2 (2%)	2 (13%)	3 (19%)	3 (50%)
Secondary diagnosis	24 (24%)	4 (31%)	2 (13%)	
mammography/fna/ ultrasound	1 (1%)			
Tru-cut biopsy	5 (5%)	4 (31%)	1 (6%)	
Fna	6 (6%)			
ultrasound	1 (1%)			
Tru-cut biopsy/ultrasound			1 (6%)	
Frozen section biopsy	8 (8%)			
Marker biopsy	3 (3%)			
Tertairy Diagnosis	2 (2%)	1 (8%)	-	
Tru-cut biopsy	1 (1%)			
Frozen section biopsy		1 (8%)		
Marker biopsy	1 (1%)			
Treatment				
Primary Surgery				
Conservative surgery	37 (36%)	3 (23%)	3 (19%)	
Mastectomy	56 (55%)	9 (69%)	6 (38%)	
Secondary surgery		2 (15%)	1 (6%)	
Conservative	2 (2%)		1 (6%)	
Mastectomy	6 (6%)	2 (15%)		
Endocrine therapy	94 (92%)	13 (100%)	15 (94%)	6 (100%)
tamoxifen	84 (82%)	11 (85%)	9 (56%)	4 (67%)
tamoxifen/megestrol	10 (10%)	2 (15 %)	6 (38%)	2 (33%)
Radical radiotherapy	41 (40%)	8 (62%)	6 (38%)	2 (33%)
Chemotherapy	8 (8%)	2 (15%)	3 (19%)	2 (33%)
Palliative radiotherapy	6 (6%)	1 (8%)	4 (25%)	2 (33%)
Palliative care	12 (12%)	5 (39%)	8 (50%)	3 (50%)
Inpatient investigation	13 (13%)	1 (8%)	4 (25%)	-
Inpatient stay for complications	2 (2%)	2 (15%)	-	1 (17%)
Oophorectomy	3 (3%)	-	-	-
Follow up				
breast clinic	97 (95%)	12 (92%)	10 (63%)	2 (33%)
radiotherapy clinic	43 (42%)	9 (69%)	10 (63%)	3 (50%)
mammography	53 (52%)	5 (39%)	3 (19%)	-
chest x-ray	36 (35%)	8 (62%)	10 (63%)	2 (33%)
spine x-ray	6 (6%)	1 (8%)	2 (13%)	1 (17%)
bone scan	27 (27%)	5 (39%)	7 (44%)	1 (17%)
ultrasound	20 (20%)	2 (15%)	2 (13%)	1 (17%)
CT scan	3 (3%)	-	2 (13%)	1 (17%)

Appendix 5.5: Resource use by stage years 1-5 - Breast cancer

YEAR 1	Stage I (n=102)	Stage II (n=13)	Stage III (n=16)	Stage IV (n=6)
Mode of Presentation				
Self	43 (43%)	8 (62%)	8 (53%)	2 (33%)
partner	1 (1%)	-	-	-
GP	14 (14%)	1 (85%)	4 (27%)	1 (17%)
screen	37 (37%)	3 (23%)	1 (7%)	1 (17%)
other	5 (5%)	1 (8%)	2 (13%)	2 (33%)
Screening				
mammography	15 (15%)	2 (15%)	1 (6%)	1 (17%)
mammography/tru-cut biopsy	2 (2%)	-	-	-
mammography/fna	13 (13%)	1 (8%)	-	-
mammography/fna/ Ultrasound	7 (7%)	-	-	-
Diagnosis				
Primary diagnosis	89 (87%)	12 (92%)	16 (100%)	6 (100%)
mammography	11 (11%)	1 (7%)	2 (13%)	-
Tru-cut biopsy	16 (16%)	2 (13%)	3 (19%)	1 (17%)
Fna	35 (34%)	4 (31%)	8 (50%)	2 (33%)
ultrasound	2 (2%)	-	-	-
mammography/fna	9 (9%)	-	-	-
fna/tru-cut biopsy	2 (2%)	-	-	-
mammography/fna/ ultrasound		1 (7%)	-	-
Frozen section biopsy	2 (2%)	1 (7%)	-	-
Marker biopsy	10 (9%)	1 (7%)	-	-
Physical examination	2 (2%)	2 (13%)	3 (19%)	3 (50%)
Secondary diagnosis	24 (24%)	4 (31%)	2 (13%)	-
mammography/fna/ ultrasound	1 (1%)		-	-
Tru-cut biopsy	5 (5%)	4 (31%)	1 (6%)	-
Fna	6 (6%)	-	-	-
ultrasound	1 (1%)	-	-	-
Tru-cut biopsy/ultrasound	-	-	1 (6%)	-
Frozen section biopsy	8 (8%)	-	-	-
Marker biopsy	3 (3%)	-	-	-
Tertairy Diagnosis	2 (2%)	1 (8%)	-	-
Tru-cut biopsy	1 (1%)	-	-	-
Frozen section biopsy	-	1 (8%)	-	-
Marker biopsy	1 (1%)	-	-	-
Treatment				
Primary Surgery				
Conservative surgery	37 (36%)	3 (23%)	3 (19%)	-
Mastectomy	55 (54%)	9 (69%)	6 (38%)	-
Secondary surgery	-	1 (8%)	-	-
Conservative	1 (1%)	-	-	-
Mastectomy	4 (4%)	1 (8%)	-	-
Endocrine therapy	94 (92%)	13 (100%)	15 (94%)	6 (100%)
tamoxifen	84 (82%)	11 (85%)	9 (60%)	4 (67%)
tamoxifen/megestrol	10 (10%)	2 (15 %)	6 (40%)	2 (33%)
Radical radiotherapy	41 (40%)	8 (62%)	6 (38%)	2 (33%)
Chemotherapy	3 (3%)	2 (15%)	2 (13%)	1 (17%)
Palliative radiotherapy	1 (1%)	1 (8%)	2 (13%)	1 (17%)
Palliative care	2 (10%)	1 (8%)	2 (13%)	3 (50%)
Inpatient investigation	11 (11%)	1 (8%)	3 (19%)	-
Inpatient stay for complications	-	2 (15%)	-	1 (17%)
Oophorectomy	3 (3%)	-	-	-
Follow up	N (% of sample) mean no of visits	N (% of sample) mean no of visits	N (% of sample) mean no of visits	N (% of sample) mean no of visits
breast clinic	96 (94%) 3	12 (92%) 3	9 (56%) 3	2 (33%) 4
radiotherapy clinic	43 (42%) 4	7 (54%) 5	10 (63%) 4	3 (50%) 3
mammography	13 (13%) 1	1 (8%) 1	1 (6%) 1	-
chest x-ray	25 (25%) 2	5 (38%) 1	9 (56%) 1	2 (33%) 2
spine x-ray	2 (2%) 1	-	1 (6%) 1	1 (17%) 1
bone scan	19 (19%) 1	3 (23%) 1	7 (44%)	1 (17%) 1
ultrasound	13 (13%) 1	1 (8%) 1	1 (6%) 1	1 (17%) 1
CT scan	1 (1%) 2	-	1 (6%) 1	1 (17%) 1

	Stage I (n=95)	Stage II (n=13)	Stage III (n=12)	Stage IV (n=3)
YEAR 2				
Treatment				
Primary Surgery				
Conservative surgery	-	-	-	-
Mastectomy	-	-	-	-
Secondary surgery	1 (1%)	1 (8%)	1 (8%)	-
Conservative		-	1 (8%)	-
Mastectomy	1 (1%)	1 (8%)	-	-
Endocrine therapy	86 (90%)	12 (92%)	12 (100%)	3 (100%)
tamoxifen	77 (81%)	10 (77%)	6 (50%)	1 (33%)
tamoxifen/megestrol	9 (9%)	2 (15 %)	6 (50%)	2 (66%)
Radical radiotherapy	-	-	-	-
Chemotherapy	2 (2%)	-	1 (8%)	1 (33%)
Palliative radiotherapy	2 (2%)	-	1 (8%)	1 (33%)
Palliative care	4 (4%)	1 (8%)	4 (33%)	-
Inpatient investigation	1 (1%)	-	-	-
Inpatient stay for complications	-	-	-	-
Oophorectomy	-	-	-	-
Follow up	N (% of sample) mean no of visits	N (% of sample) mean no of visits	N (% of sample) mean no of visits	N (% of sample) mean no of visits
breast clinic	72 (76%) 2	9 (69%) 2	5 (42%) 2	1 (33%) 1
radiotherapy clinic	35 (37%) 3	9 (69%) 3	7 (58%) 3	2 (66%) 3
mammography	24 (25%) 1	1 (8%) 1	-	-
chest x-ray	6 (6%) 1	3 (23%) 1	2 (17%) 4	1 (33%) 1
spine x-ray	2 (2%) 1	1 (8%) 1	-	-
bone scan	3 (3%) 1	1 (8%) 1	2 (17%) 1	-
ultrasound	3 (3%) 1	-	1 (8%) 1	-
CT scan	-	-	1 (8%) 2	-
YEAR 3	**Stage I (n=86)**	**Stage II (n=11)**	**Stage III (n=7)**	**Stage IV (n=2)**
Treatment				
Primary Surgery				
Conservative surgery	-	-	-	-
Mastectomy	-	-	-	-
Secondary surgery	1 (1%)	-	-	-
Conservative	1 (1%)	-	-	-
Mastectomy	-	-	-	-
Endocrine therapy	78 (91%)	9 (82%)	7 (100%)	2 (100%)
tamoxifen	70 (81%)	8 (73%)	4 (57%)	1 (50%)
tamoxifen/megestrol	8 (9%)	1 (9 %)	3 (43%)	1 (50%)
Radical radiotherapy	-	-	-	-
Chemotherapy	2 (2%)	-	-	-
Palliative radiotherapy	2 (2%)	-	1 (14%)	-
Palliative care	3 (3%)	3 (27%)	2 (29%)	-
Inpatient investigation	-	-	1 (14%)	-
Inpatient stay for complications	1 (1%)	-	-	-
Oophorectomy	-	-	-	-
Follow up				
breast clinic	64 (74%) 2	6 (55%) 1	3 (43%) 2	-
radiotherapy clinic	36 (42%) 4	6 (55%) 3	4 (57%) 4	2 (100%) 3
mammography	26 (30%) 1	1 (9%) 1	2 (29%) 2	-
chest x-ray	5 (6%) 1	2 (18%) 1	1 (14%) 1	-
spine x-ray	1 (1%) 1	-	-	-
bone scan	7 (8%) 1	3 (27%) 1	-	-
ultrasound	4 (5%) 1	1 (9%) 1	-	-
CT scan	1 (1%) 1	-	-	-
YEAR 4	**Stage I (n=76)**	**Stage II (n=7)**	**Stage III (n=4)**	**Stage IV (n=1)**
Treatment				
Primary Surgery	1 (1%)	-	-	-
Conservative surgery	-	-	-	-
Mastectomy	1 (1%)	-	-	-
Secondary surgery	1 (1%)	-	-	-
Conservative	-	-	-	-
Mastectomy	1 (1%)	-	-	-
Endocrine therapy	68 (89%)	7 (100%)	4 (100%)	1 (100%)
tamoxifen	62 (81%)	7 (100 %)	2 (50%)	-
tamoxifen/megestrol	6 (8%)	-	2 (50%)	1 (100%)
Radical radiotherapy	-	-	-	-
Chemotherapy	1 (1%)	-	-	-
Palliative radiotherapy	1 (1%)	-	-	-
Palliative care	3 (4%)	-	-	-
Inpatient investigation	1 (1%)	-	-	-
Inpatient stay for complications	1 (1%)	-	-	-
Oophorectomy		-	-	-
Follow up				
breast clinic	51 (67%) 2	4 (57%) 1	1 (25%) 1	-
radiotherapy clinic	31 (41%) 2	4 (57%) 2	3 (75%) 2	1 (100%) 3
mammography	17 (63%) 1	2 (29%) 2	-	-
chest x-ray	3 (4%) 1	2 (29%) 1	-	-
spine x-ray	1 (1%) 1	-	-	-
bone scan	3 (4%) 1	-	-	-
ultrasound	5 (7%) 1	-	-	-
CT scan	1 (1%) 1	-	-	-

YEAR 5	Stage I (n=31)	Stage II (n=3)	Stage III (n=1)	Stage IV (n=1)
Treatment				
Primary Surgery	-	-	-	-
Conservative surgery	-	-	-	-
Mastectomy	-	-	-	-
Secondary surgery	-	-	-	-
Conservative	-	-	-	-
Mastectomy	-	-	-	-
Endocrine therapy	-	-	-	-
tamoxifen	31 (100%)	3 (100%)	1 (100%)	-
tamoxifen/megestrol	-	-	-	1 (100%)
Radical radiotherapy	-	-	-	-
Chemotherapy	-	-	-	-
Palliative radiotherapy	-	-	-	-
Palliative care	-	-	-	-
Inpatient investigation	-	-	-	-
Inpatient stay for complications	-	-	-	-
Oophorectomy	-	-	-	-
Follow up	-	-	-	
breast clinic	5 (16%) 1	1 (33%) 2	-	-
radiotherapy clinic	15 (48%) 2	2 (67%) 2	1 (100%) 1	1 (100%) 2
mammography	5 (16%)	-	-	-
chest x-ray	1 (3%)	-	-	-
spine x-ray	-	-	-	-
bone scan	1 (3%)	1 (33%)	-	-
ultrasound	1 (3%)	-	-	-
CT scan	-	-	-	-

Appendix 5.6 Assumptions for the breast cancer screening model

- The assumption was made that the effect of incidence screening is to improve the staging distribution at diagnosis, with no effect on cancer yield .
- In 1991 (reference year), 106,172 women were invited for screening,
- 81,694 attended,
- 5,825 were recalled for further investigation[Trent Breast Screening Quality Assurance Reference Centre, 1996 #325].
- The unit cost of screening was taken to be the average cost of mammography as employed in our earlier estimate (£22).
- An estimate of £7 per woman invited for administration costs, was provided by the Nottingham screening unit[Nottingham City Hospital Breast Screening Unit, 1996 #326].
- Assessment costs were calculated from the audit of the medical notes of screened patients. The costs were £49, £37, £22 and £22 for stages I through IV.
- In 1991 (reference year) there were 2,687 new breast cancer registrations in the Trent region. Of the cancers in the sample, 32 per cent had been detected as a result of screening, 46 per cent were self detected, whilst the remainder were discovered primarily through examinations by general practitioners. The distribution of cancers by stage was 74, 10 12 and 4 per cent for stages 1 through 4, respectively.
- For the screening scenario it was assumed that the 2,687 cancers presented or were detected according to the above stage distribution.
- For the no-screening scenario, it was assumed that these cancers would have presented according to the staging distribution of those cancers not detected by screening. This was 68,11,16 and 5 per cent for stages I through IV, respectively. As expected this latter distribution for the no-screen scenario was comparatively inferior from the prognostic point of view.

Chapter 6

Cervical Cancer

6.1 Introduction

In the UK invasive carcinoma of the cervix uteri (otherwise known as cervical cancer) accounts for two per cent of all cancer registrations in women. It is the eighth most common cancer in women. The disease is rare below the age of twenty, but increases rapidly to peak in the 35-39 year age group. There then follows a slight decline in rates followed by another rise, peaking at a slightly higher rate in the 65-69 age groups, then declines once again (Figures 6.1 & 6.2). With respect to this bimodal distribution in age-specific incidence, cervical cancer is unusual. The age-specific incidence rates demonstrate the cohort effect of those women born in the 1920's having higher rates of cervical cancer throughout their lives(1). There has been an increase in the number of registrations in the under 35 age group, it represents the most common cancer for women aged 20-35 years, with 25 per cent of all cancer registrations in this age group being attributable to cervical cancer. Registrations of these invasive cancers represent a combination of symptomatic and screen-detected cases, screening has the effect of advancing the age at diagnosis. Therefore, it may be that the trend in age-specific incidence in young women is an artefact of the screening programme. However, it is believed that a true increase in this age group has occurred and that the reason for it is the disease's associated risk factor. It is thought that the genital wart virus, human papilloma virus (HPV), may be a causal factor

for cervical cancer in young women. Recently there has been increased research into screening for HPV and developing diagnostic tests(2, 3).

Before becoming invasive, cervical cancer progresses through a pre-malignant stage of the disease, cervical intraepithelial carcinoma (CIN), segregated into grades 1 to 3, (CIN I-III). CIN III is coded as carcinoma-in-situ (CIS). The Cancer Registries and therefore the Office for National Statistics only record cases of CIN III/CIS. As for invasive carcinoma, there has been an increase in the age-specific registration rates for the 15-44 age groups. The rate per 1000 female population in Trent has increased from 0.39 in 1979 to 1.26 in 1994, peaking at 1.49 in 1990. These registration figures are an underestimate of the true incidence of CIS as the disease is asymptomatic and can only be detected by screening. In fact these figures are actually a mixture of the prevalence, in women being screened for the first time, and incidence of the disease. Only where women are screened every year are these figures a true representation of the actual incidence.

From the most recent registration and mortality figures, invasive cancer of the cervix uteri accounts for:

- 3,400 new registrations in England and Wales in 1992 (Figure 6.1)(4).
- 229 new registrations in the Trent region in 1997 (Figure 6.2)(5).
- There has been a significant increase in the number of registrations for invasive cervical cancer and carcinoma-in-situ in young women (Figures 6.3 & 6.4).
- 1,339 deaths in England and Wales in 1997(6) (Figure 6.5)
- 133 deaths in Trent in 1997.
- The 5-year relative survival rate is 60% in England and Wales, and 65% in Trent. However, survival is directly related to stage at the time of diagnosis. For those diagnosed at an early stage the survival rate is much higher at nearly 80%, while those diagnosed at a very advanced stage fare less well with survival rates of less than 10%(7, 8).
- 18,409 registrations of carcinoma in situ (CIS) of the cervix in 1992(4), this figure includes those with cervical intraepithelial carcinoma grade 3 (CIN III) (Figure 6.6).
- 1,868 registrations in Trent in 1997.
- 85% of all CIN III registrations are incurred by women aged 20-44 years of age (Figure 6.7).

Figure 6.1 Number and age-specific cervical cancer registrations, England and Wales 1992

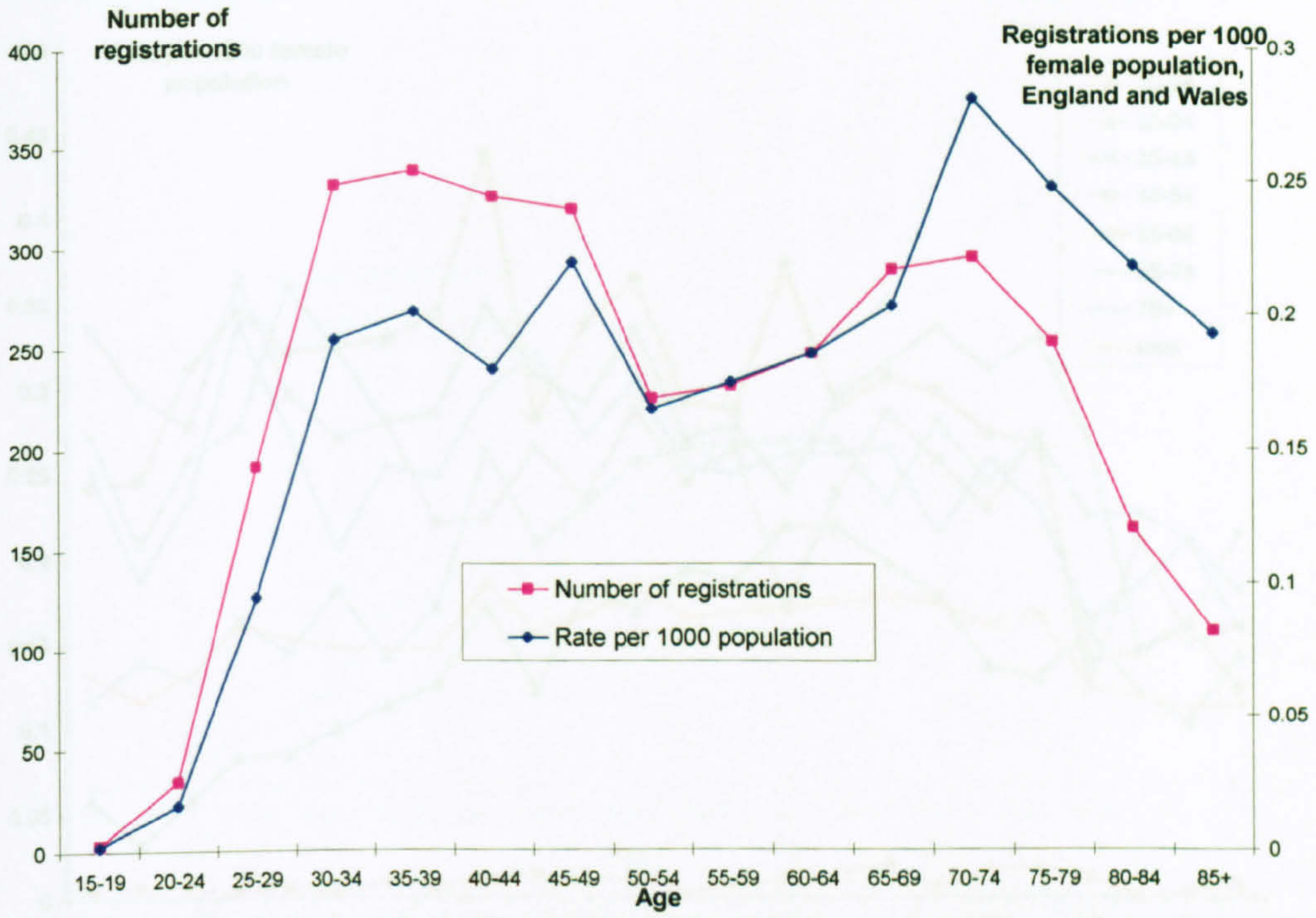


Figure 6.2 Number and age-specific cervical cancer registrations, Trent 1994

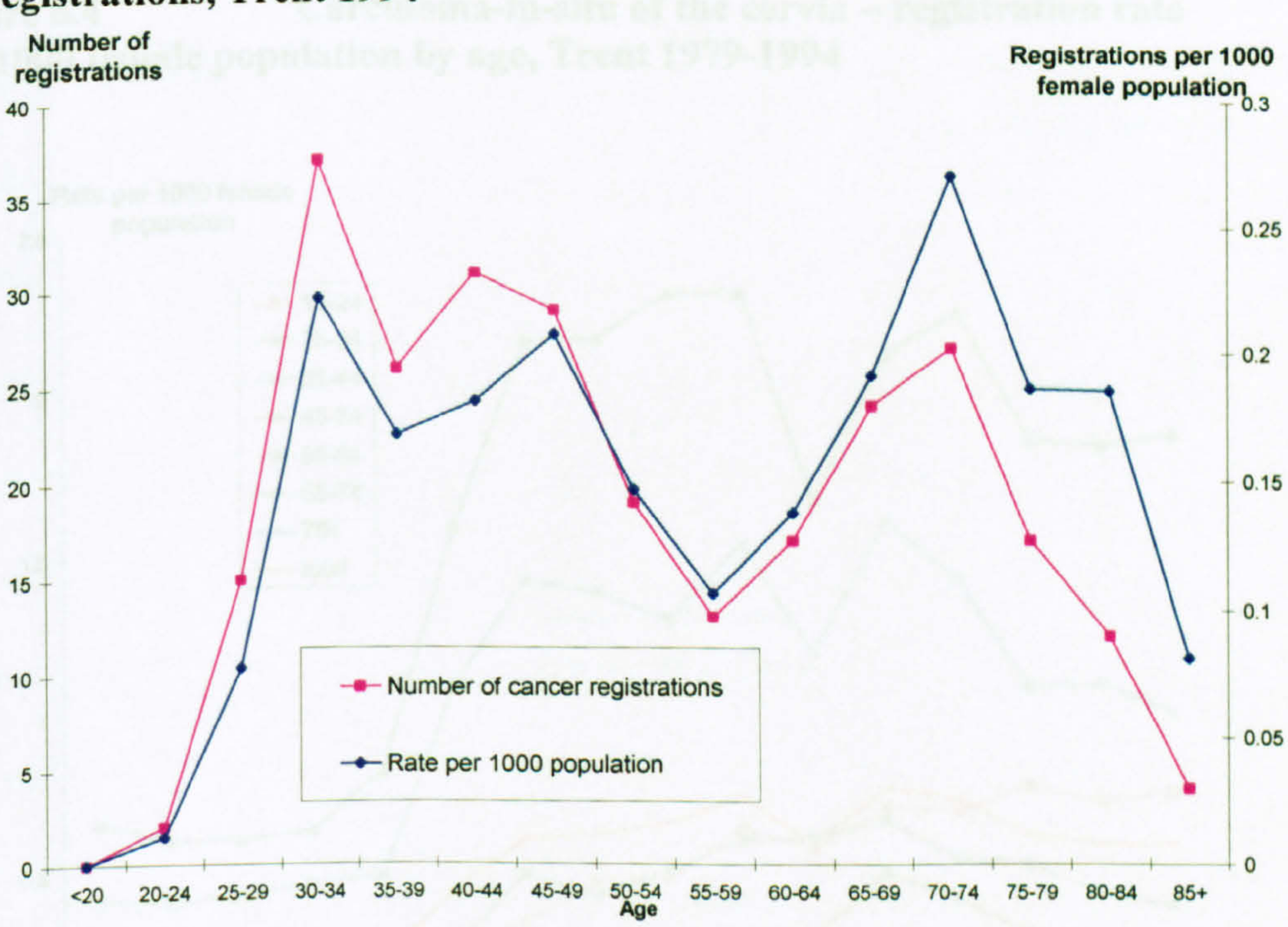


Figure 6.3 Cancer of the cervix uteri – registration rate per 1000 female population by age, Trent 1971-1994

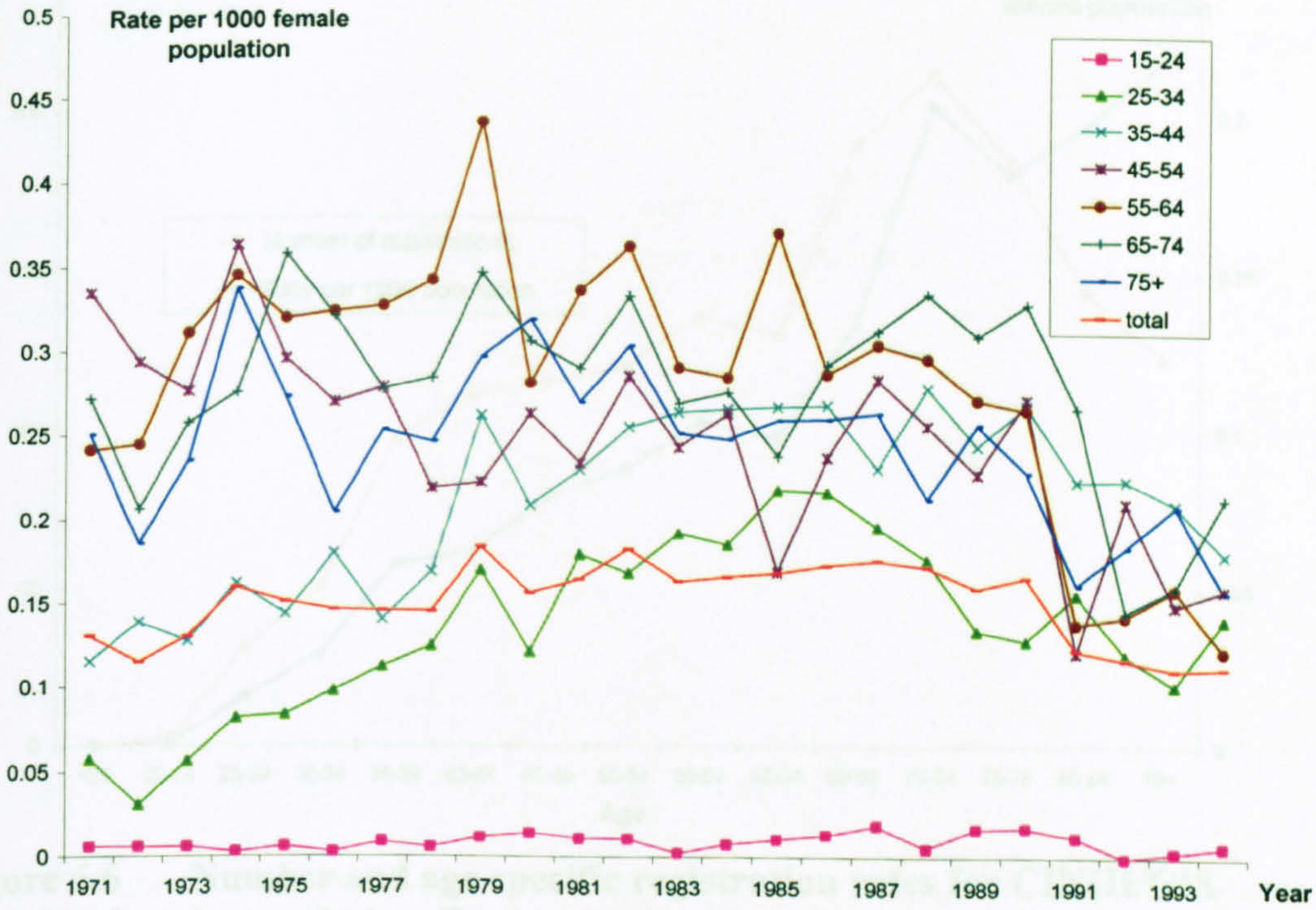


Figure 6.4 Carcinoma-in-situ of the cervix – registration rate per 1000 female population by age, Trent 1979-1994

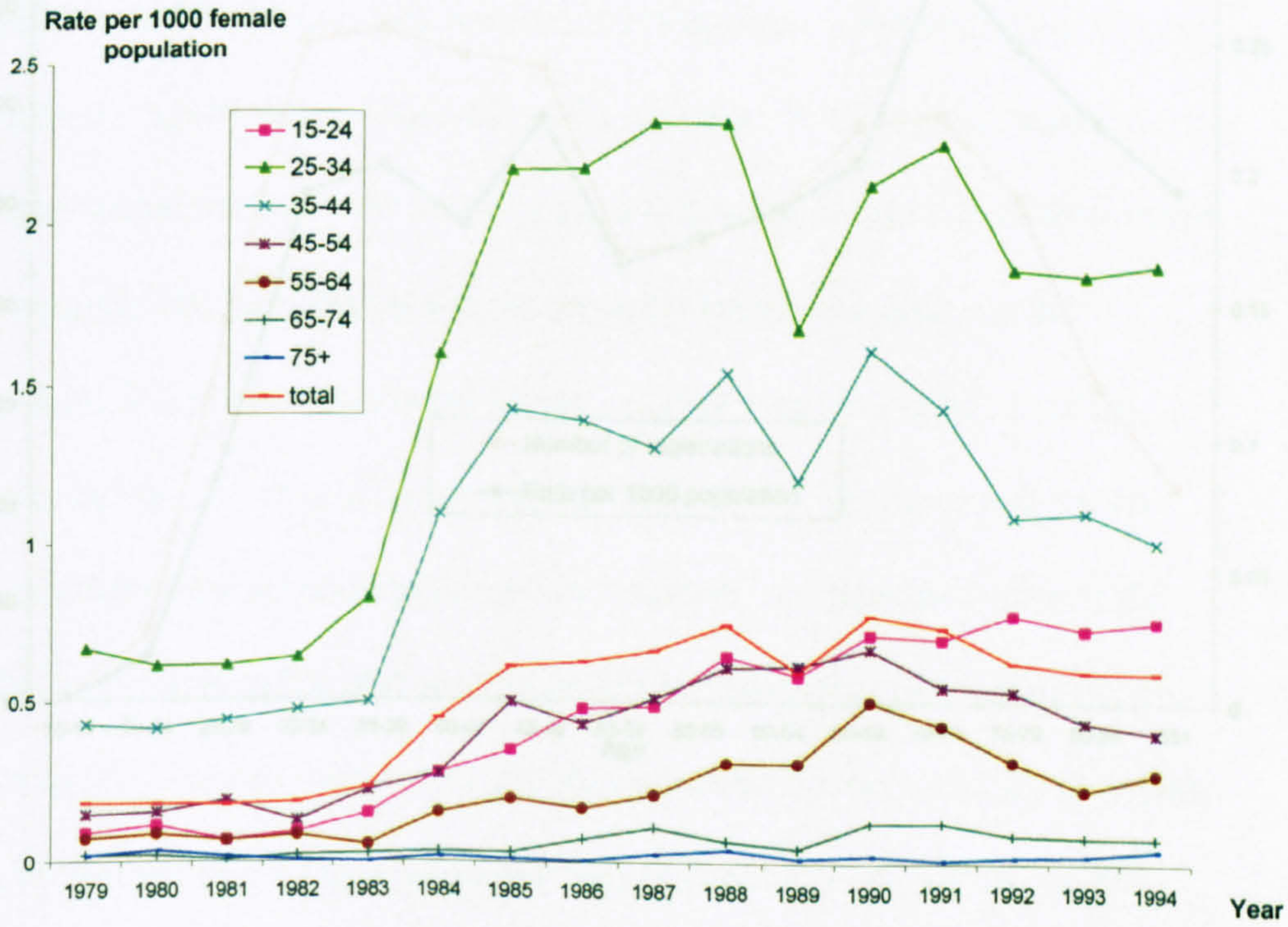


Figure 6.5 Number and age-specific cervical cancer mortality rates per 1000 Female Population, England and Wales, 1992

Figure 6.6 Number and age specific registration rates for CINIII/CIS per 1000 female population, England & Wales 1992

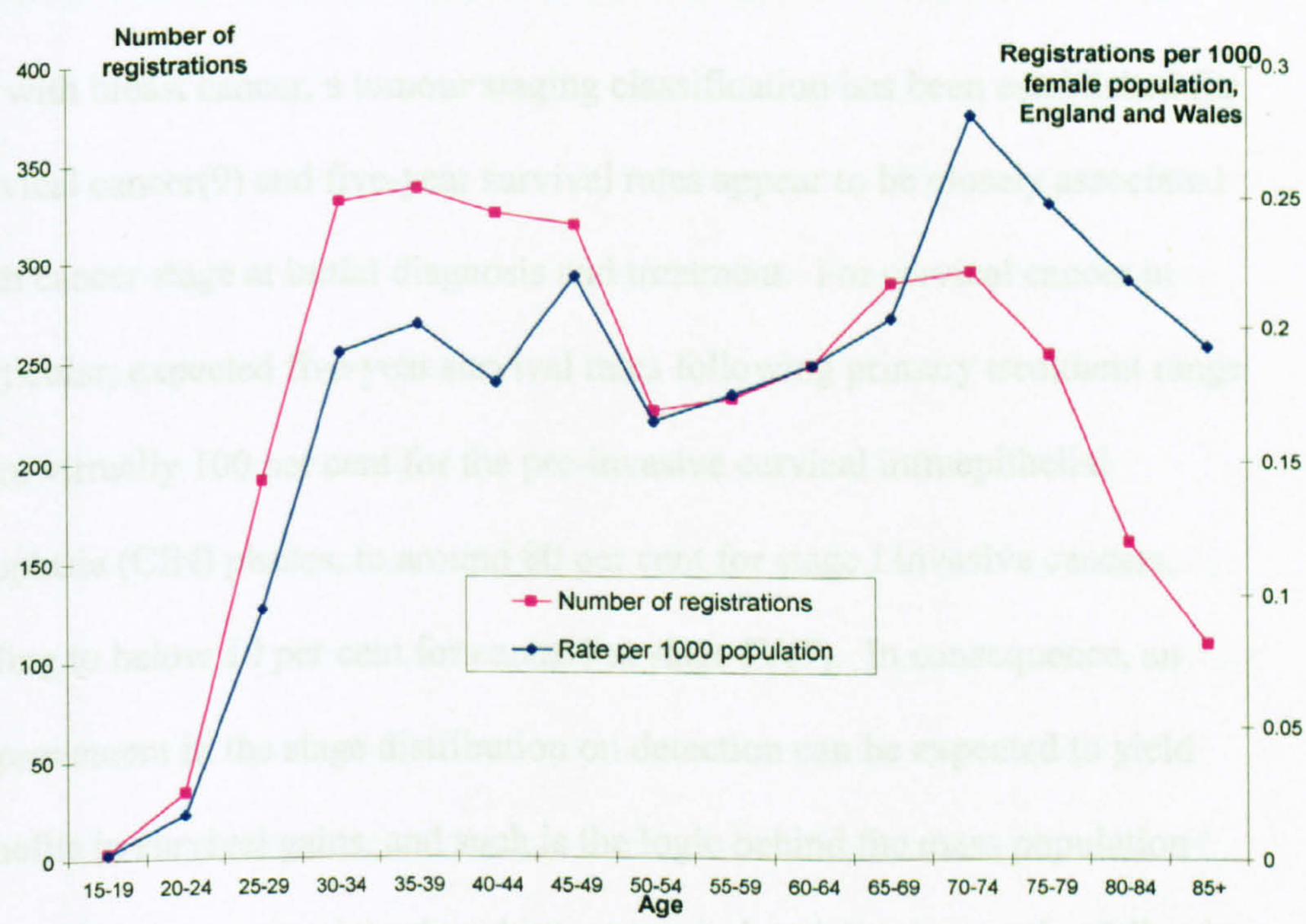
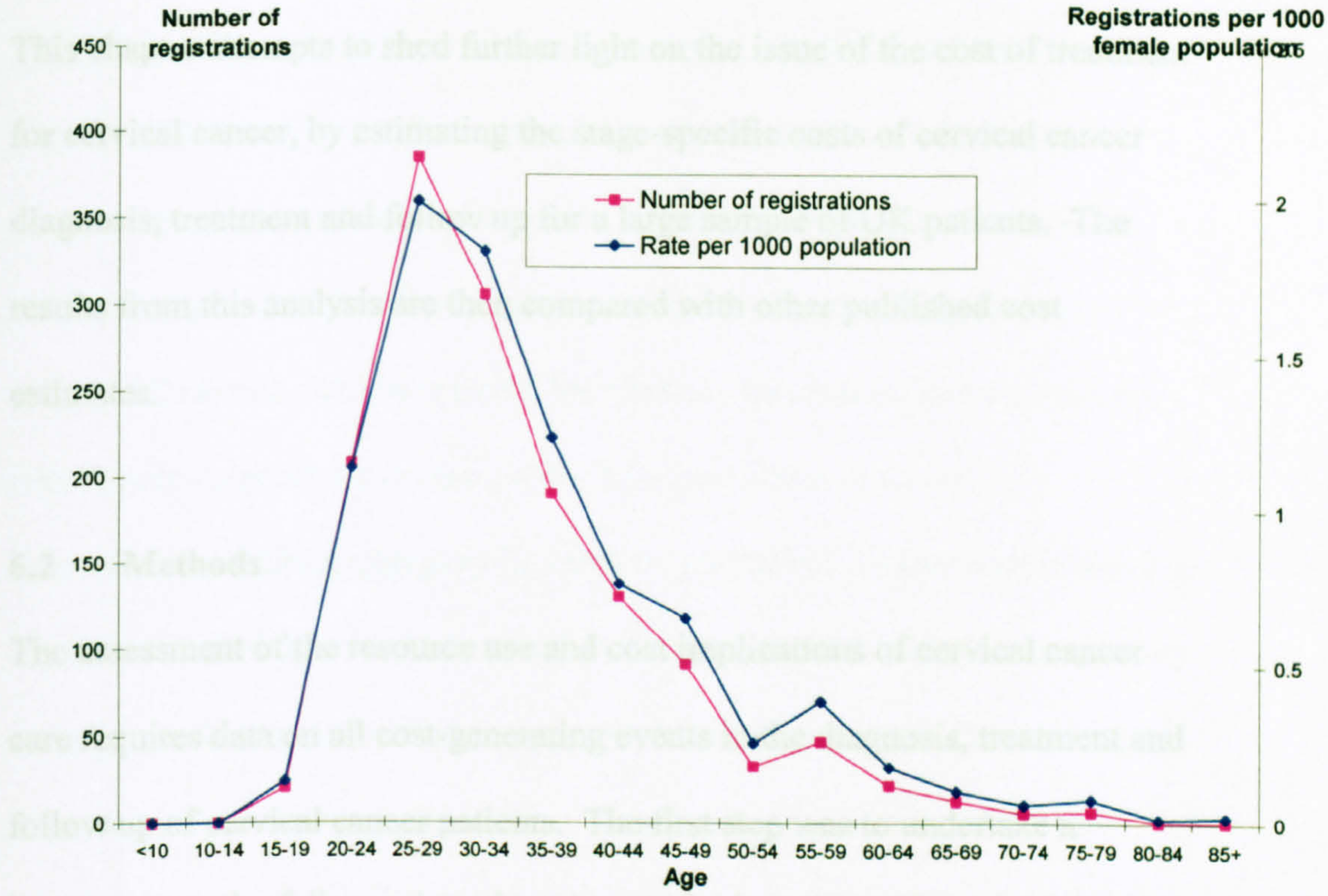


Figure 6.7 Number and age specific registration rates for CINIII/CIS per 1000 female population, Trent 1994



As with breast cancer, a tumour staging classification has been established for cervical cancer(9) and five-year survival rates appear to be closely associated with cancer stage at initial diagnosis and treatment. For cervical cancer in particular, expected five-year survival rates following primary treatment range from virtually 100 per cent for the pre-invasive cervical intraepithelial neoplasia (CIN) phases, to around 80 per cent for stage I invasive cancers, falling to below 10 per cent for cancers at stage IV(7). In consequence, an improvement in the stage distribution on detection can be expected to yield benefits in survival gains, and such is the logic behind the mass population screening programmes introduced into many industrialised countries following the development of the Papanicolaou (Pap) smear test in the 1940s. In the United Kingdom, the screening programme is thought to have relieved the

burden of incidence of invasive cancers that might otherwise have occurred, especially amongst younger-to-middle-aged women(10).

This chapter attempts to shed further light on the issue of the cost of treatment for cervical cancer, by estimating the stage-specific costs of cervical cancer diagnosis, treatment and follow up for a large sample of UK patients. The results from this analysis are then compared with other published cost estimates.

6.2 Methods

The assessment of the resource use and cost implications of cervical cancer care requires data on all cost-generating events in the diagnosis, treatment and follow up of cervical cancer patients. The first step was to undertake a literature search of diagnosis and treatments for invasive and pre-invasive cervical cancer. Details were primarily taken from Chomet *et al.* (1989) for pre-invasive cancer(11) and Dickson (1980), Brenner (1982), Coulter and Mason (1990), Sproston (1994) and Kingston (1985) for invasive carcinoma of the cervix(12-16).

This information was used to construct stage specific treatment algorithms (basic algorithms are presented in Appendix 6.1). These literature based treatment algorithms were useful in the development of a proforma to be used for obtaining information on cervical cancer resource use from the medical notes of all patients diagnosed with cervical cancer in Trent in 1990 (Appendix 6.2).

6.2.1 Treatment for pre-invasive and invasive cervical cancer - Literature

Diagnosis: All pre-invasive and most of invasive cervical carcinomas will usually be detected by the Pap smear. These patients along with those presenting symptomatically will require further investigations to assess the extent and spread of the disease and to aid in the staging of the disease.

All patients will be referred for clinical examination and the majority will require colposcopic investigation. This involves a stereoscopic microscope providing a brightly illuminated magnified dimensional image and requires a skilled operator. A smear may be taken from the cervix for cytology and a punch biopsy taken if there is an obvious lesion present. A cone biopsy may be performed if the lesion is small enough to excise completely, this involves the surgical excision of a wedge-shaped circular section of the cervix.

Rectovaginal examination must be performed in all patients to assess the possible parametrial and posterior tumour spread. If the cancer proves to be invasive there is a need to exclude any spread of the tumour beyond the confines of the cervix. Pyelography (IVP) is essential, particularly in cases where the tumour has spread beyond the cervix. Obstruction of the ureter is a clear sign of infiltration of the parametrial tissue. This is of particular importance prior to surgery. Other investigations involve lymphangiography; to assess spread to the lymph nodes and aid the planning of radiotherapy, scanning and ultrasound, for example CT scanning.

Mandatory investigations include a full blood count, urea and electrolytes, liver function tests, intravenous urogram and chest radiography. An examination under anaesthesia should then be performed. Rectovaginal

examination should be repeated in order to clinically stage the tumour. If there is any suspicion of rectal spread, proctoscopy and sigmoidoscopy are performed. Cystoscopy is not considered essential in patients who have early stage disease but must be performed if the disease appears to be locally advanced. For example, at the time of the examination under anaesthesia when the biopsy is being taken it might be convenient to examine the bladder by way of a cystoscope to check for bladder involvement.

Treatment - CIN: Before treatment, there is a need to rule out the existence of invasive carcinoma. The Pap smear is repeated, then colposcopic investigation, endo-cervical curettage, and colposcopically directed cervical biopsy for the more advanced cases.

Treatment usually consists of either a full cone biopsy, laser ablation or cryosurgery to remove any abnormal epithelium, after which no further treatment is usually necessary. In some cases simple hysterectomy might be recommended. In all cases, follow up smears are mandatory.

Treatment - Early stage invasive carcinoma (stage I & IIa): The mainstay of treatment is surgery and/or radiotherapy. Wertheim hysterectomy is the most common form of hysterectomy carried out in current practice, it consists of an en bloc dissection of the uterus, vagina and parametria. In addition the pelvic lymph nodes are dissected. Post-operative complications do exist, the most frequent being uretero-vaginal fistulae in approximately 3% of patients. Radiation therapy tends to be a combination of intracavity implants and external therapy. External therapy is given by high energy X-rays from a linear accelerator administered at a dose of approximately 160-200 rads per day, total dose of approximately 4000/5000 rads in 4-6 weeks. It is given to

control the spread within the pelvis and treat the pelvic lymph nodes, and can also contribute to tumour control. Therefore it is usually given prior to intra-cavity radiotherapy (ICT). Complications from radiotherapy involve the bladder, rectal ulceration, fistula formation, colitis, fractures, vaginal necrosis, etc. These occur in 5-10% of patients.

Neither surgeons nor radiotherapists can claim any statistical superiority of either treatment, the 5 year survival rate in the UK whatever the modality is 80% for stage I, and 60% for stage IIA (17).

Treatment - Advanced carcinoma of the cervix (stage IIb, III and IV):

Radiotherapy is generally the treatment of choice. If the patient is fit this should be radical and not necessarily palliative.

Involvement of the bladder or rectum is not necessarily a death sentence and unless clinical examination reveals evidence of blood or bone metastasis or lymphatic involvement, radical radiotherapy should be indicated. If the disease has metastasised then palliative care is required.

To date no chemotherapeutic regimen has had significant impact on this type of cancer, although short remissions have been induced by a combination of vincristine, bleomycin and mitomycin-C.

Follow up: Careful follow up of all patients for cancer of the cervix is essential. This includes clinical examination and regular smears to check for early signs of recurrence.

Recurrence: For local recurrence, further radiotherapy may be justified, although there is a risk of necrosis and fistula formation. Chemotherapy may be given to those patients who have already received surgery and radiation therapy, this treatment is mostly palliative. The most common sites of

recurrence are the pelvis (83% of cases), cervix (29%), bladder (23%), parametria (10%), pelvic wall (10%). The risk of recurrence diminishes each year after treatment and by the fifth year the mortality of the patients treated for cervical cancer is the same as for the normal population(12).

6.2.2 Estimation of treatment costs

The ideal method for costing any disease process is to have resource use and cost information on a patient specific basis. Given that the epidemiology of cancer in the UK has long been documented by the Cancer Registries on such a patient specific basis, it might be thought that a population-based resource use audit could be easily accomplished using pre-collected data. However, the Registry databases do not usually include details of either resource use or cancer stage at diagnosis. The treatment cost analysis was accordingly based on a detailed examination of the case notes of 336 invasive cervical cancer patients treated in the Trent region (central England). This was facilitated by the use of a proforma developed with the aid of information obtained from the initial literature review on diagnosis and treatment (see Appendix 6.2). It was verified by a consultant in obstetrics and gynaecology based at the City Centre, Nottingham, and piloted on 50 medical notes of cervical cancer patients treated at the same hospital.

The 336 cervical cancer patients used for the cost analysis were obtained from the population of 378 individulas in the12 districts covered by the Trent Cancer Registry. Of this original sample, 42 patients had to be excluded on the grounds of missing notes, no information in the notes, incorrect diagnosis, duplication or being diagnosed outside the chosen year of 1991 (Table 6.1).

Table 6.1 Cervical cancer sample: retrieval of medical notes and exclusion of patients (by district of primary treatment)

			Excluded:				
District	No of case notes retrieved	Not found	Duplicate	Recurrence	No information	Not cancer	Not diagnosed in 1990
N Derbyshire	21	3	-	-	-	3	2
S Derbyshire	31	2	-	-	-	1	2
Leicester	47	4	-	-	-	4	1
N Lincs	15	-	1	-	-	-	-
S Lincs	15	1	-	1	-	-	-
Bassetlaw	12	-	-	-	-	-	-
Central Notts	23	-	-	-	-	-	-
Notts	71	2	-	-	-	1	2
Barnsley	24	-	-	-	-	-	-
Doncaster	44	-	-	-	-	1	-
Rotherham	20	-	-	-	2	3	-
Sheffield	38	3	1	1	-	-	-

Of the 336 patients who met with the inclusion criteria, for 76 (23%) there was insufficient information to enable the staging of their cancers. The patient numbers were 128, 76, 41 and 15 for stages I through IV, respectively (Table 6.2).

Table 6.2 Total sample size used for cost estimation by stage

Stage	Number	Percentage	Stage	Number	Percentage of staged cancers
Ia	20	6%	I	128	49%
Ib	81	24%			
I	28	8%			
IIa	24	7%	II	76	29%
IIb	40	12%			
II	12	4%			
IIIa	4	1%	III	41	16%
IIIb	22	7%			
III	15	4%			
IVa	1	0%	IV	15	6%
IVb	1	0%			
IV	13	4%			
Unstaged	76	23%			
Total	336				

All the patients in the sample had been diagnosed with cervical cancer in 1990. This particular year was selected on the grounds that it permitted me to construct a resource audit for each patient over a minimum of 59 months and a maximum of 77 months follow up from diagnosis. The analysis of the cost data was based on a five-year follow up time horizon, a period following diagnosis during which the majority of cancer recurrences would be likely to occur(12). Imputation of cost data was undertaken for those patients who did not have full cost histories for this period (excluding those who had died or been discharged) using monthly averages based on the previous 12 months data. The sample demographic and resource use data were entered into SPSS for Windows version 6 on a patient specific and anonymous basis. From the individual patient records, stage-specific algorithms of diagnostic and therapeutic events entailing costs were developed.

The unit costs of these events were obtained from a survey of eleven of the region's principal service providers, each of whom was sent a form

requesting the cost of the various activities, as performed at their site (Table 6.3) (a 100% response rate was achieved following persistent contacts with key finance personnel). Since 1993, all National Health Service (NHS) providers have been required to follow a uniform accounting protocol, requiring that their services be costed at full cost, i.e. all service-specific variable costs, with the inclusion of the relevant components of fixed and overhead costs (NHS Management Executive, 1993). The mean of the reported costs was employed for each event, converted back to 1990 prices using the NHS pay and price index. Given that management events were occurring across time, the cost of events occurring in year 2 onwards, following diagnosis were discounted at 6 per cent. In other words, mean five-year costs were expressed as a 1990 present value, to represent the prospective cost implications from the perspective of the baseline year.

By combining the unit cost estimates with the resource use information, the mean costs of diagnosis, treatment and follow-up by stage at diagnosis for the sample over the follow up period were obtained. For comparative purposes costs were also split into three distinct disease phases; initial care, continuing care and terminal care costs. Initial treatment costs included all the costs initiated within the first 3 months from diagnosis and also calculated again using a longer phase of the first 6 months of treatment. Terminal care costs were calculated using the last 3 months of costs for patients who had died during the follow up period. These were also calculated again using a longer phase of the last 6 months of treatment and care. Continuing care costs were obtained by calculating the average monthly cost incurred after the initial 3 months following diagnosis and in cases where

death occurred prior to the final 3 months of care used in estimating the terminal care costs. Again, continuing care costs were also calculated taking account of the 6-month initial costs and 6-month terminal costs.

Table 6.3 Unit costs of diagnosis, treatment and follow-up events (£ sterling 1990 prices)

Event	Outpatient cost (£)	Day-case cost (£)	Inpatient cost (£)
Smear	43.35		
Colposcopy	48.25	173.95	239.98
Punch biopsy	40.00	198.06	257.02
Cone biopsy	23.53	238.73	269.44
Loop excision	43.31	239.75	255.78
Laser ablation		250.00	250.00
D & C	45.00	199.27	221.47
Cystoscopy	39.13	178.78	194.97
Chest x-ray	9.23		
IVP	61.79	122.12	122.12
Proctoscopy	43.31	170.08	166.73
Sigmoidoscopy	43.31	177.02	260.77
Ultrasound	21.10		
CT scan	57.36		
MRI scan	123.72		
Liver scan	38.01		
Abdominal x-ray	10.50		
Kidney x-ray	27.38		
Pelvic x-ray	10.63		
Bone scan	57.07		
Liver function test	38.01		
Laparotomy	43.31	177.02	260.77
Polypectomy	43.31	177.02	260.77
Total conservative hysterectomy			188.85
Radical wertheims hysterectomy			195.25
Colostomy			196.26
Inpatient stay (per day)			180.96
Outpatient visit	37.27		
Inpatient palliative care (per day)			145.50
Hormone replacement therapy (per month)	3.49		
Histopathology	13.66		
Cytology	8.87		
Biochemistry	4.73		
Haematology	4.95		
Microbiology	5.99		

Table 6.3 (continued)

Radiotherapy costs 1990 prices (£ sterling)

Radiotherapy Type	Cost per attendance (£)	Cost per episode (£)
Low energy:	60.35	
1-4 fractions		227.20
5-10 fractions		568.00
Simple:	63.90	
1-4 fractions		639.00
5-10 fractions		1902.80
11-15 fractions		3422.20
16-25 fractions		5197.20
Simple with simulation:	67.45	
1-4 fractions		639.00
5-10 fractions		1917.00
11-15 fractions		3457.70
16-25 fractions		5239.80
Complex with simulation:	74.55	
16-25 fractions		3790.80
25+ fractions		6517.80
Complex with technical support:		
16-25 fractions		5339.20
25+ fractions		6688.20
Brachytherapy		1079.20

Chemotherapy costs 1990 prices (£ sterling)

Cytotoxic Drug	Dosage	Cost (£)
Bleomycin	15 units/15mg	12.71
Ifosfamide	500mg	6.05
	1g	10.53
	2g	19.44
Cisplatin	10ml/10mg	4.02
	50ml	20.07
	100ml	40.13
Doxorubicin	10mg	14.60
	50mg	73.01
Methotrexate	1ml	1.51
	2ml	2.10
	4ml	4.01
	8ml	8.02
	20ml	20.05
	40ml	35.65
	200ml	160.45
Carboplatin	5ml	17.83
	15ml	53.48
	45ml	160.45
Mitomycin	2mg	4.93
	10mg	16.22
	20mg	30.94

Unfortunately the sample of 336 patients only included those diagnosed with invasive carcinoma of the cervix. In order to ascertain any cost savings brought about by a shift in the stage distribution of the cancers due to the national screening programme, some idea of the resource use and cost of pre-invasive carcinoma was required. The regional cancer registry holds records only for CIN III cases, although details of management are not included. Thus the information was obtained from a consultant gynaecologist who has kept a record of all women seen at his colposcopy clinic at Queens Medical Centre, Nottingham, since June 1990. Notes were kept of all diagnostic, management and follow up information. All women seen at the colposcopy clinic had been referred as a result of an abnormal smear, and following further colposcopic investigation could be deemed either to have no abnormality, CIN I, CIN II or CIN III.

Information for all patients seen at the colposcopy clinic from June 1990 to June 1991 was abstracted. 221 women were seen at the colposcopy clinic during this period, although not all of these were diagnosed as having pre-invasive cancer (see Table 6.4). Women found to have no abnormality or diagnosed with invasive cancer were excluded from further analysis. 114 pre-invasive cancers were detected. The total costs of pre-invasive disease were estimated in the same way as for invasive cervical cancer, using the resource-use of all CIN I-III patients and the unit costs from the finance departments.

Table 6.4 Results of case note retrieval – pre-invasive cancer

Findings	n	% of total sample
No abnormality	57	25
CIN I	15	7
CIN II	31	14
CIN III	95	43
Invasive	6	3
Missing information	17	8
Total	221	-

6.3 Results

6.3.1 Sample characteristics

The sample characteristics by stage at diagnosis are displayed in Table 6.5. Approximately fifty per cent of the sample present with stage I disease, while six per cent present with stage IV disease. The mean age at diagnosis for the sample of patients diagnosed with invasive cervical cancer was 54 years. A one-way analysis of variance indicates that mean age at diagnosis differs significantly according to the stage of the disease ($F = 8.930$, $P = 0.000$), with late stage cancers diagnosed in older women. Sixty-one percent of the sample was still alive at the time of data collection. This corresponds with the national 5-year survival rate of 60%(7).

Table 6.5 Sample characteristics

Stage	No (%)	Mean age at diagnosis (sd)	No. deceased at abstraction (%)	No alive at abstraction (%)
I	128 (49%)	50 (14.18)	17 (13%)	111(87%)
II	76 (29%)	54 (16.42)	41 (54%)	35 (46%)
III	41 (16%)	60 (15.20)	29 (70%)	12 (30%)
IV	15 (6%)	67 (15.45)	13 (87%)	2 (13%)
Total	260	54 (15.74)	100 (39%)	160 (61%)

Table 6.6 depicts the mode of presentation of patients in the sample. Of the cancers in the patient sample the majority had been self detected (49 %), 35

per cent had been screen detected, 9 per cent had been detected by GPs or in the genito-urinary (GU) clinic. The remainder (7 %) were detected through other means, mostly by being admitted to accident and emergency departments with abdominal pains.

Table 6.6 Mode of presentation of cervical cancer patients by stage at diagnosis

Stage	Self detected	GP	Screen	GU clinic	Other
I	42 (33%)	9 (7%)	72 (56	2 (2%)	3(2%)
II	50 (66%)	2 (3%)	19 (25%)	1 (1%)	4 (5%)
III	30 (73%)	5 (12%)	0	1 (2%)	5 (12%)
IV	5 (33%)	2 (13%)	1 (7%)	0	7 (47%)
Total	127 (49%)	18 (7%)	92 (35%)	4 (2%)	19 (7%)

6.3.2 Resource Use

Invasive cancer: Considerable diversity with respect to cost-events was evident on a patient-by-patient basis. For example, a total of 22 distinct diagnostic events were found to have occurred amongst the 261 cases, including cytology, colposcopy and various X-rays and scans. In some cases, many or all of the diagnostic events were undertaken on an inpatient basis whilst, in others, some or many of the tests were administered on an outpatient or day-case basis, with differential consequences for costs. Surgery was of two types, namely, Wertheim's and conservative hysterectomy, whilst radiotherapy was palliative or radical, external beam, intracavity or combination. Patient-specific radiotherapy costs varied with type (e.g. low energy, simple, complex), number of fractions and setting (e.g. inpatient or outpatient). Post-primary treatment, each patient received one or more of up to 18 forms of immediate procedure or further investigation, for example,

investigation for fistulae, blood transfusion or emergency inpatient admission. Within the sample, 7 different chemotherapy drugs were employed, in combinations, dosages and settings specific to each of the patients so treated. Appendix 6.3 presents the treatment resource-use by tumour stage for the invasive cervical cancer patient sample. To enable detailed costing and allow for discounting, this resource-use was estimated by the year in which it was incurred (see Appendix 6.4).

One of the most significant factors contributing to the cost of cancer care is the cost of hospitalization. Table 6.7 outlines the average length of stay for stages I to IV by therapeutic procedure. No difference in the proportion of patients by stage undergoing inpatient diagnosis exists, although the mean length of stay increases according to stage progression. This can be explained by the requirement of more investigations performed to assess the spread of the disease in late stage cancers. In-patient stays for surgery are more prevalent for stage I cancers compared with stage II and III cancers, however this is an effect of a greater proportion of stage I patients having surgery. No major difference in inpatient stay or length of stay exists between cancer stages for chemotherapy or investigations. Stage I, II and III cancers show higher rates of inpatient episodes for primary radical radiotherapy than for stage IV cancers, again explained by the treatment specification for these patients. This is also the case with inpatient palliative care and palliative radiotherapy where the prevalence of inpatient episodes and average length of stay increase with stage severity.

Following initial treatment for the cancer significant burdens of care are again incurred when a patient suffers a recurrence or disease progression

(regional recurrence or metastasis). Table 6.8 displays the recurrence and disease progression by stage of the disease at diagnosis.

Table 6.7 Inpatient length of stay, by cancer stage – Invasive cervical cancer

	Stage I (128)				Stage II (76)				Stage III (41)				Stage IV (15)			
	n	%	mean LOS	SD	n	%	mean LOS	SD	n	%	mean LOS	SD	n	%	mean LOS	SD
Diagnosis	96	75	4.9	6.1	60	79	9.1	14.5	33	79	11.1	11.2	8	53	15.5	17.0
Wertheim's hysterectomy	57	45	11.5	3.6	19	25	12.2	3.2	2	3	10.5	0.7	-	-	-	-
Total hysterectomy	14	11	7.6	2.6	3	4	28.0	24.8	-	-	-	-	-	-	-	-
Chemotherapy	4	3	13.5	12.5	9	12	9.0	6.2	5	12	10.8	5.1	-	-	-	-
Primary Radical radiotherapy	29	45	21.5	14.4	49	65	24.4	17.4	27	62	24.0	15.2	2	13	31.5	5.0
Primary Palliative radiotherapy	1	1	29.0	-	2	2	32.5	3.5	6	14	18.2	8.7	8	53	34	7.2
Investigation	23	18	23.0	34.0	30	39	21.5	43.5	11	26	29.9	28.4	4	27	25.5	37.9
Inpatient palliative care	8	6	18.1	14.4	25	33	30.6	40.4	15	36	32.4	49.3	8	53	56.6	75.2

n = number of patients by stage experiencing inpatient stays
% = percentage of patients by stage experiencing inpatient stays
Mean LOS = the average length of stay in days

Table 6.8 **Recurrence and disease progression by stage at diagnosis for the cervical cancer sample**

	All	Stage I	Stage II	Stage III	Stage IV
Local recurrence	52 (20%)	10 (8%)	28 (37%)	14 (34%)	-
Metastasis	26 (10%)	4 (3%)	12 (16%)	5 (12%)	5 (33%)
Site of metastasis		Lung (3)	Bone (4)	Liver (2)	Lung (1)
		Pelvis (1)	Lung (6)	Kidney (1)	Liver (2)
			Liver (2)	Brain (1)	CNS (2)
				Spine (1)	

Pre-invasive cervical cancer: Appendix 6.5 presents the treatment resource-use by tumour stage for the pre-invasive cervical cancer patient sample. Understandably, the range of diagnostic, management and follow-up events for the pre-invasive cancers was comparatively narrow, being confined to smears, colposcopy and biopsies (11 distinct events in total). No inpatient episodes were required for any of the patients and all were discharged within one year of treatment.

6.3.3 Treatment costs

Table 6.9 presents the results of the cost analysis for the invasive cancer patients. For the sample data, one-way analysis of variance (Duncan multiple range test at 5 per cent) suggests that the mean total cost of diagnosis, treatment and follow up for stage I cancers is significantly lower than that for cancers at the other three stages. The proportions of the total costs incurred in the first year following diagnosis were 78, 76, 88 and 98 per cent, for stages I through IV, respectively. With such high proportions, the impact of discounting on mean historic costs is small, undiscounted costs are £6,716, £11,127, £10,980 and £11,548 for stages I to IV respectively.

Within the sample, stage I costs for diagnosis, radiotherapy, chemotherapy, investigations and inpatient palliative care were significantly lower than those for stages II through IV. Grouping the two principal palliative cost categories (palliative radiotherapy and inpatient palliative care) together, stage IV palliative costs were significantly higher than those for stages II and III, and all three were higher than those for stage I. Grouping the primary treatment cost categories (surgery, radical radiotherapy, investigations, hormone replacement and chemotherapy), stage IV primary treatment costs were significantly lower than those of stages II and III, whilst I costs were lower than those of stage II. A further analysis of cost by therapeutic regimen (surgery vs. non-surgery) was conducted on the 126 stage I and 68 stage II patients where interventions were intended to be curative rather than palliative. For these stage I cancers, 57% received surgery, with a mean five-year cost of £5,839 (all palliative treatments excluded). The corresponding mean cost for those treated non-surgically was significantly higher at £7,967 (t-test, $P = 0.01$). For stage II cancers, 32% proceeded via surgery, at a mean cost of £10,478. The mean cost for those treated non-surgically, £12,261, was not significantly higher (t-test, p=0.45). Sample sizes for the remaining stages were too small to enable comparisons to be made.

The pre-invasive cancer sample comprised 15, 31 and 95 cases at CIN1 through CIN3, respectively. The differences between mean costs for the management of pre-invasive carcinomas at each of these grades were insubstantial (< 1%).

Averaged across all the CIN grades the mean cost of management was estimated at £386 (SD 66) (Table 6.10). This comprised costs of diagnosis (19% of the total mean cost) - including initial smear, colposcopy (13%) and punch biopsy – costs of

treatment (62%) -including loop cone (44%), knife cone (10%) and laser biopsies - and costs of follow-up (19%), entailing further smears, colposcopy and biopsies. Analysis of variance revealed that the mean total cost of pre-invasive carcinoma of the cervix was significantly lower than that for all stages of invasive cancer ($F = 90.06$ $P = 0.000$).

In clinical management terms, the significant cost differential between stage I cervical cancer and that at more advanced stages may be explained as follows. Stage I cervical cancer requires fewer staging investigations to assess the extent of tumour spread at the time of diagnosis. The treatment of choice tends to be hysterectomy with adjuvant radical radiotherapy. In turn, such radiotherapy is less complex and is more regularly carried out on an outpatient basis. Due to superior prognosis, fewer post-primary treatment investigations are undertaken and less palliative radiotherapy and palliative inpatient care is necessary.

As is evident from the standard deviations presented in table 6.9, cost variations about the mean for particular classes of events are high, with standard deviations often exceeding the means. Such a pattern is commonly observed when cohorts are costed and arises because of wide variations in treatment patterns between patients, even amongst those ostensibly exhibiting the same pattern of disease. Spread is inevitably enhanced when, as is often the case, a proportion of the cohort receives no treatment under a particular cost heading, i.e. zero costs are included in the range. It will be observed in tables 6.9 and 6.10 that, whilst certain individual items of therapy display large variances, the variance in the total is substantially smaller. This

is accounted for by negative correlations between costs in the different categories, principally, the palliative/primary sub-divisions as noted above.

The costs reported exclude the time and travel costs incurred by the patient and their family when undergoing any of the treatment. When these costs, based on estimates reported by Sculpher and colleagues(18) updated to 1990 costs, are included, the estimated management costs for cervical cancer increase by 4.7%, 3.0%, 2.3%, 1.9% and 1.3% for pre-invasive to stage IV cancers respectively.

For the purpose of comparison with the breast cancer data and with other cervical cancer cost estimates(19) it is useful to observe costs according to three distinct disease phases, initial, continuing and terminal disease. Table 6.11 displays these cost data. The initial care costs have been calculated using the first three and six months of care. The terminal care costs have been taken to be the costs incurred three months and six months prior to death. Continuing care costs are based on average monthly costs of continuing care. For the sample as a whole, mean initial, continuing and terminal care costs estimated over a 3-month period amount to £5,831, £82 and £4,089 respectively, over a 6-month period they amount to £6,169, £81 and £5,809 respectively.

Table 6.9 Five-year costs of diagnosis, treatment and follow-up, by stage (£ 1990)

	Stage I			Stage II			Stage III			Stage IV		
	Mean	SD	% of total	Mean	SD	% of total	Mean	SD	% of total	Mean	SD	% of total
Diagnosis	1,481	1,546	22.4	2,401	3,479	22.0	2,894	2,902	26.7	2,621	3,991	22.7
Surgery	1,159	1,177	17.5	795	1,594	7.3	100	448	0.9	-	-	0.0
Radical radiotherapy	2,295	2,704	34.7	3,817	2,597	35.0	3,683	2,826	34.0	946	2,509	8.2
Palliative radiotherapy	79	540	1.2	203	904	1.9	700	1,628	6.5	2,727	2,951	23.6
Chemotherapy	75	506	1.1	367	1,031	3.4	257	734	2.4	-	-	0.0
Hormone replacement therapy	39	71	0.6	37	65	0.3	3	16	0.0	-	-	0.0
Investigations	719	2,790	10.9	1,457	5,129	13.4	1,369	3,349	12.6	1,208	3,811	10.5
Inpatient palliative care	150	733	2.3	1,267	3,509	11.6	1,478	4,567	13.6	3,841	9,326	33.3
Follow-up	626	342	9.5	566	420	5.2	354	382	3.3	192	363	1.7
TOTAL	6,623	4,753	100.0	10,910	9,076	100.0	10,838	7,121	100.0	11,535	11,724	100.0
(95% CI)	(5,789 - 7,452)			(8,837 - 12,985)			(8,590 - 13,085)			(5,042 - 18,027)		
Un-discounted total costs	*6,718*	*4,856*		*11,127*	*9,409*		*10,980*	*7,143*		*11,548*	*11,725*	

Table 6.10 Cost of pre-invasive carcinoma of the cervix

		CIN I (15)			CIN II (31)			CIN III (95)		
		Mean	SD	% of total	Mean	SD	% of total	Mean	SD	% of total
Diagnosis	Smear	2	4	0.5	1	2	0.5	1	3	0.5
	Colposcopy	52	13	13	48	-	13	48	-	12
	Punch biopsy	32	27	8	34	21	9	19	20	5
Management	Loop cone biopsy	128	124	33	178	107	47	174	108	45
	Knife cone biopsy	-	-	-	15	60	4	53	100	14
	Laser biopsy	83	122	21	40	94	11	23	66	6
Follow up	Smear	42	12	11	31	22	8	30	19	7
	Second smear	3	11	0.5	1	8	0.5	5	15	1
	Third smear	-	-	-	-	-	-	1	5	0.5
	Colposcopy	42	17	11	23	25	6	31	23	8
	Biopsy	8	17	2	3	10	1	3	10	1
TOTAL COST		**392**	**89**		**375**	**59**		**388**	**64**	
	95% CI	343-441			353-396			375-402		

Table 6.11 Cost of initial, terminal and continuing care

Cost £	All		Stage I		Stage II		Stage III		Stage IV	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Initial 3 month*	5,831	4,062	4,644	2,951	6,635	4,406	7,697	3,959	8,672	7,653
Terminal 3 month**	4,089	5,674	2,094	2,987	3,599	4,727	5,184	6,777	5,703	7,695
Continuing 3 month***	82	302	50	163	123	387	39	51	478	1,082
Initial 6 month+	6,169	3,877	5,030	3,081	7,531	4,559	7,449	3,179	9,682	5,862
Terminal 6 month++	5,809	7,527	3,192	4,320	4,401	6,405	7,571	8,302	9,313	10,157
Continuing 6 month+++	81	477	79	555	98	392	44	59	18	16

*Initial treatment costs include all the costs initiated within the first 3 months from diagnosis
**Continuing care costs are calculated using the average monthly cost incurred after the initial 3 months following diagnosis and in cases where death occurred prior to the final 3 months of care used in estimating the terminal care costs
***Terminal care costs were calculated using the last 3 months of costs for patients who had died during the follow up period
+Initial treatment costs include all the costs initiated within the first 6 months from diagnosis
++Continuing care costs are calculated using the average monthly cost incurred after the initial 6 months following diagnosis and in cases where death occurred prior to the final 6 months of care used in estimating the terminal care costs
+++Terminal care costs were calculated using the last 6 months of costs for patients who had died during the follow

6.4 Impact of costs with respect to Trent region

In addition to the 376 invasive cancers identified in the Cancer Registry data, 1,867 cases of pre-invasive cancer were detected in 1990, as a result of the screening programme. Assuming that the full population of invasive cancers was staged according to the sample stage distribution, the gross 1990 discounted five-year costs of the management of cervical cancer in Trent would amount to approximately $4.1 million, equivalent to slightly less than £1 per head of population (see Table 6.12). For cervical cancers as a whole, the invasive cases comprised just 16 per cent of the total, yet were responsible for 83 per cent of the costs of diagnosis, treatment and follow-up. Sizeable cost economies in the management of cervical cancer may evidently be realised by detection at earlier stages; for example, had all the invasive cancers been detected at stage I then the total diagnosis and treatment costs for Trent would have been around 21 per cent lower. Perhaps more improbably, had all the cancers been detected by screening at the pre-invasive stage, then the total diagnosis and treatment costs for Trent would have amounted to only around £0.9m, representing a saving of £3.3 million or 79 per cent of cervical cancer management costs. Naturally, these potential treatment cost savings would have to be offset against the costs of the screening programme.

Table 6.12 Impact of cost of cervical cancer in Trent

Stage	Stage distribution	Number of cancers	Average cost estimate £1990	Total cost £1990
CIN III/CIS	82%	1,867	338	631,046
Stage I	8%	195	6,621	1,291,095
Stage II	5%	115	10,910	1,254,650
Stage III	3%	64	10,838	693,632
Stage IV	1%	24	11,535	276,840

6.5 Comparison with other cervical cancer costing studies.

The results of this analysis of cervical cancer management costs can be compared with those of other studies (Table 6.13). One undertaken in the USA (20) produced figures for stage I cancer of around £6,000 (converted into £ 1990 using exchange rates and up-rating using the Hospital and Community Health Services Pay and Price Index) and, for stage IV, of around £10,000. However, unlike my results, stage II and III costs were closer to those of stage I than they were to those of stage IV. Another US study produced significantly lower cost estimates for invasive cervical cancer ranging from £3600-£7,100(21). A later US study (22) cited results with a closer similarity to the Trent estimates - stage I at around £7,000 with stages II through IV at £11-12,000 - whilst another (23) produced translated estimates of around £5,500 for early-stage, and of around £8,000 for late-stage, cancer. The study by Mandelblatt and colleagues produced similar cost estimates to the Trent estimates, with estimates converted to 1990 £ sterling of £930 for carcinoma-in-situ, £5,500 for early stage cancer and £10,400 for advanced stage cancer(24). Unfortunately the methods used for costing were not described in detail and limited any thorough comparisons. A more recent US study exploring the costs and cost-effectiveness of screening for cervical cancer in HIV-infected women used significantly higher cost estimates for pre-invasive (£900-£3,800) and invasive (£13,200-£19,100) cancer(25). Significantly higher cost estimates were also used by two more US studies when estimating the cost-effectiveness of PAPNET testing(26) and interactive neural network assisted screening(27). In a New Zealand study(28) the average treatment costs for all invasive cancers across all stages was estimated at around £6,500. A French study

estimated the costs of pre-invasive cancer at £480, early stage cancer ranging from £1,500-£5,900 and late stage cancer at £14,000(29). A Dutch study resulted in similar cost estimates to those reported in this thesis for invasive disease, stage I was estimated to range from £5,100 to £11,052, and £10,500 for stages II-IV(30). Similar results were also reported in a US study where costs were estimated according to initial and terminal care costs (based on a six month basis)(19). The reported initial and terminal costs were, for local disease £6,600 (compared with the Trent cost estimate of £5,000), for regional disease £8,500 and £5,700 (compared with Trent cost estimates of £7,500 and £6,000), and for distant disease £9,300 and £10,800 (compared with the Trent cost estimates of £9,700 and £9,300).

Suggestive as these findings are, it must be borne in mind that the comparison of cost results across health care systems is intrinsically problematic. Currency conversions are essentially arbitrary and, especially in the USA, charges and prices are frequently used in place of resource costs. Perhaps most importantly, none of the above studies provide either sufficient detail of the methods of cost-accounting employed, or information at a disaggregated level, to enable the reader to identify the sources of similarities and differences between their estimates and those reported in this thesis. The following studies however, are more transparent:

One early UK study(31) employed a case record approach to costing and examined 80 pre-invasive and invasive cases. Converted into 1990 prices, the estimates were £376 and £1,969 per case, respectively, and the pre-invasive estimate corresponds closely with the Trent figures. The invasive estimate, however, is considerably lower, and this is accounted for by the use of a one-year, rather than five-

year, time frame, the omission of many chemotherapy and radiotherapy costs and the use of, in my view, an unrealistically-low estimate of inpatient hospital stay (less than 10 per cent of the values observed in the Trent data, even after allowance for inflation). A more recent study (32), which used only length of stay as an indicator of resource usage for invasive cancer, produced an order-of-magnitude estimate of £3,000 per case per annum (1990 prices), i.e. £15,000 over five years. Cuzick and colleagues (1999) (33) in a review of the role of HPV testing, estimated the costs of CIN and invasive cancer, the cost estimates for stage I and advanced disease closely approximate the Trent cost estimates, however the costs for pre-invasive (£900) and stages II and III cancers (£6,000) differ.

Of the existing studies, the two that come closest to those reported in this thesis, in terms of methodology, were based in Holland. That which assessed the cost of management of invasive cancer at stages III and IV (34) produced an estimate in local currency that translates to £9,034, proximate to the Trent estimate of around £10,500. However, that which assessed the cost of CIN III pre-invasive carcinomas (35) produced an estimate of £1,153 in 1990 prices. This figure is considerably higher than my estimate, yet the transparency of the Dutch study permits an explanation of the difference, which derives essentially from variations in patient management between the samples. In the Dutch study, 33 per cent of women had conservative treatment (laser ablation, cryotherapy and loop diathermy), 56 per cent had conization with an average length of inpatient stay of 2.7 days and 11 per cent underwent hysterectomy, with an average length of stay of 1.3 days. In the Trent sample, however, no CIN3 case underwent hysterectomy, 95 per cent had conization and only

5 per cent had conservative treatment. Neither of these last two procedures required inpatient stays as all were carried out on either an outpatient or day-case basis. This comparison clearly indicates that, whilst costs inevitably differ within a health care system on a patient-by-patient basis, systematic cost differences can be observed across health care systems, owing to the acceptance of different management protocols.

Table 6.13 Studies estimating cervical cancer costs

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK £ 90
Baker et al. 1987(22)	US	Medicare data	Medicare charges	US $	Not stated	Initial therapy:		(Assume 1987 prices)
						CIS	$5,641	£3,684
						Stage I	$11,600	£7,576
						Stage II	$16,891	£11,032
						Stage III	$16,891	£11,032
						Stage IV	$18,587	£12,139
Bethwaite et al 1986(28)	New Zealand	Literature review		New Zealand $	1984	Dysplasia/ CIN	$337	£190
						CIS	$2,183	£1,226
						Invasive cancer	$11,734	£6,596
Cuzick et al 1999(33)	UK	Screening: 1988 annual report of cervical cancer screening at Watford General Hospital, Curative primary treatment and advanced disease Thames Cancer Registry	Screening: 1988 annual report of cervical cancer screening at Watford General Hospital, Management of CIN from NHS price tariff for HRG. Curative primary treatment from van Ballegooijen et al. 1997(30)	UK £	Not stated	Low grade CIN	£790	-
						High grade CIN	£1,150	
						Curative primary treatment:		
						IA	£2,970	
						IB	£6,000	
						II+	£6,000	
						Advanced disease	£9,590	

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK £ 90
El M'Rini et al. 1997(29)	France	Retrospective review of 24 hospital records in radiotherapy department	Not able to tell as only English abstract available	French Francs	1995	First year costs:		
						CIS	5,023 FF	£484
						IA	15,867 FF	£1,529
						IB-IIA	61,540 FF	£5,931
						IIB-IV	145,314 FF	£14,004
Fahs et al. 1992(23)	US	National Hospital Discharge Survey	Medicare charges	US $	1988	CIN	$1,102	£663
						CIS	$4,359	£2,624
						Early invasive stage	$9,216	£5,548
						Late invasive stage	$13,359	£8,041
Goldie et al, 1999(25)	US	From algorithm developed by Muller et al. 1990(36)	Medicare charges	US $	1996	CIN I	$1,118 (559-1677)	£937
						CIN II & III	$4,597 (229-6896)	£3,852
						Invasive (40% stage I, 60% stage II, III IV)	$15,759-22,843 (7880-34260)	£13,207-19,143
Helms et al. 1999(19)	US	Washington state HMO	HMO expenditures	US $	1996	Local:		
						Initial#	$15,759	£6,628
						Continuing*	$3,907	£1,643
						Terminal**	-	-
						Regional:		
						Initial#	$20,406	£8,583
						Continuing*	$641	£270
						Terminal**	$13,747	£5,782
						Distant:		
						Initial#	$22,127	£9,307
						Continuing*	$59,422	£24,993
						Terminal**	$10,988	£10,988
Mandelblatt et al 1997 (24)	US	Based on various literature sources	From hospital finance department	US $	1992	CIN I & II	$178	£96
						CIS	$1,718	£931
						Local stage	$10,162	£5,507
						Regional stage	$17,616	£9,546
						Advanced stage	$19,272	£10,444

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK £ 90
Radensky and Mango 1998(27)	US	Used model of care by developed by Eddy(37)	Medicare fee schedules	US $	1997	CIS	$9,156	£4,042
						Stage I	$18,828	£8,313
						Stage II	$27,416	£12,104
						Stage III	$27,416	£12,104
						Stage IV	$30,168	£13,319
Schecter 1996(26)	US	Used treatment algorithms developed by Muller et al(36)	Used median charges submitted by fee for service physicians to indemnity insurance plans and hospital charges set by Health Care Financing administration	US$	1994	Low grade CIN	$1,944	£996
						High grade CIN	$9,528	£4,884
						Early invasive stage	$23,015	£11,797
						Late invasive stage	$34,270	£17,556
Schneider and Twiggs 1972(20)	US	Accounts department of the University of Michigan Medical Center	Charges from the accounts department of the University of Michigan Medical Center	US $	1971	Stage I	$2,477	£6,670
						Stage II	$2,250	£6,059
						Stage III	$2,855	£7,688
						Stage IV	$4,060	£10,933
Smucker et al. 1979(21)	US	1,844 women at Anderson Hospital and Tumor Institute, Texas	Not stated	US $	1977	Local	$2,100	£3,622
						Regional	$3,065	£5,286
						Distant	$4,126	£7,116

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK £ 90
Thorn et al. 1975(31)	Scotland	Case notes of 80 patients diagnosed in 1971	Estimated costs for consumables, IP day, ward care, operating theatre, investigations and drugs	UK £	1971	Pre-invasive Invasive carcinoma	£93 £487	£376 £1,969
van Ballegooijen et al. 1992(34)	Netherlands	Hospital care: number of admissions and LOS national hospital database, number and type of procedures from medical notes of 40 women who died from cervical cancer. Nursing home care: National dataset covering 80% of nursing homes. Home care: National district nursing association data based on 4% of Dutch population	Hospital and nursing home care: actual resource costs, nursing cost per day, radiotherapy costs from breast cancer study. Home care: average wages per type of carer.	Dutch Guilders Dfl	1990	Advanced disease	29,200 Dfl	£9,034

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK £ 90
		population						
Ballegooijen et al. 1995(35)	Netherlands	Used PALGA connected to cytopathology labs – all women with CIN 1987-1990. Inpatient procedures from national dataset. Outpatient procedures from responses from 10% of hospitals	Colposcopy and inpatient day: actual resource costs were used, all other procedures used the tariffs charged.	Dutch Guilders Dfl	1993	CIN I & II CIN III	2,572 Dfl 3,727 Dfl	£796 £1,153
Ballegooijen et al. 1997(30)	Netherlands	Did not state, this was part of a study modeling the cost-effectiveness of HPV testing	Used costs charged in the Netherlands	Dutch Guilders Dfl	1995	IA IB II+	9,500 Dfl 20,200 Dfl 19,100 Dfl	£5,198 £11,052 £10,449
Waugh and Robertson 1996(32)	UK	Admissions and length of stay based on Scottish inpatient statistics	Cost per inpatient day based on charges at two Scottish hospitals	UK £	1990	Invasive carcinoma cost per annum	£3,000	£3,000 per annum

initial care costs = first six months' costs
* continuing care costs = indefinite duration
*** terminal care costs = last six months' costs

6.6 Conclusions

At the time of planning the analysis of the costs for cervical cancer in the Trent region, only one rather out-dated UK cost study existed(31). Cost estimates from other countries were available, however, again the majority were from studies conducted in the 1970s and 1980s(20-22, 28). Even where cost estimates were available for current years of analysis(23, 34), variations in treatment protocols and ways of estimating costs through the use of charges make it problematic to transfer the results to a UK setting. It was surprising to find that no formal cost-effectiveness analysis of the screening programme has ever been undertaken in the UK. However, this lack of analysis is due to the lack of available data from the UK cervical screening programme. The screening programme was introduced in the mid 1960's based on the prior hypothesis that screening would reduce the incidence and mortality of invasive cervical cancer. A hypothesis based on little evidence let alone any randomised control trial. The UK programme led a haphazard existence until the mid 1980's (see Appendix 6.6 for explanation of the UK cervical cancer screening service since 1984), and is blamed for the continually high rates of invasive cancer incidence and mortality in the UK compared with other countries where screening has been in place. As Draper (1982) states:

"When compared with the performance of services in some other countries, and with computed expectations in this country, the UK screening service appears to be a relative failure." (38:39).

Due to the length of time the screening programme has existed in the UK, no data exist on incidence rates or stage distribution prior to the implementation of the

programme. It was therefore felt impossible to use the cost estimates reported in the chapter to analyse the cost-effectiveness of the UK cervical screening programme. However, analysis of the cost-savings relating to altering the current distribution of stage at diagnosis was undertaken.

This cost analysis has therefore provided current estimates of cost for cervical cancer by stage of disease. It suggests that the mean total cost of diagnosis, treatment and follow up for stage I cancers is significantly lower than that for cancers at the other three stages, and that cost of pre-invasive cancer is significantly lower than that for invasive cancer. For cervical cancers as a whole, the invasive cases comprised just 16 per cent of the total, yet were responsible for 83 per cent of the costs of diagnosis, treatment and follow-up. Sizeable cost economies in the management of cervical cancer may evidently be realised by detection at earlier stages; for example, had all the invasive cancers been detected at stage I then the total diagnosis and treatment costs for Trent would have been around 21 per cent lower. Perhaps more improbably, had all the cancers been detected by screening at the pre-invasive stage, then the total diagnosis and treatment costs for Trent would have amounted to only around £0.9m, representing a saving of £3.3 million or 79 per cent of cervical cancer management costs. Naturally, these potential treatment cost savings would have to be offset against the costs of the screening programme.

The estimation of these costs is extremely pertinent to the current research into HPV testing. Before such a programme can be introduced, the National Health Service requires evidence of its effectiveness and cost-effectiveness. Modeling work has already been undertaken using Dutch cost estimates(30, 33). However two new

trials have recently been funded using the cost estimates reported in this chapter to explain the potential cost savings involved in implementing HPV testing.

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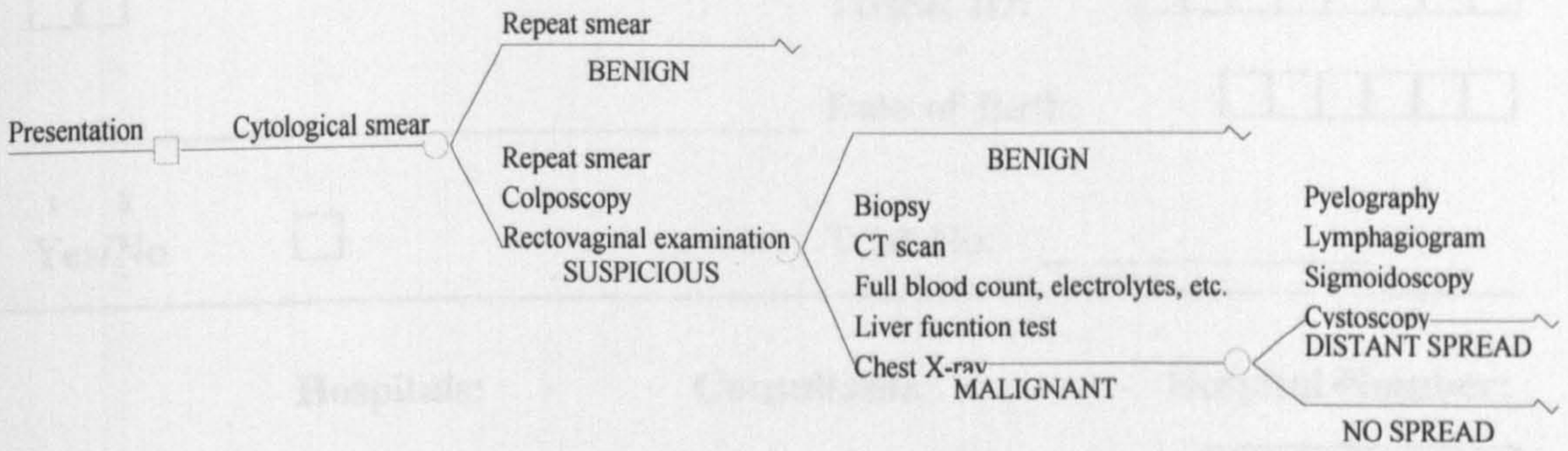
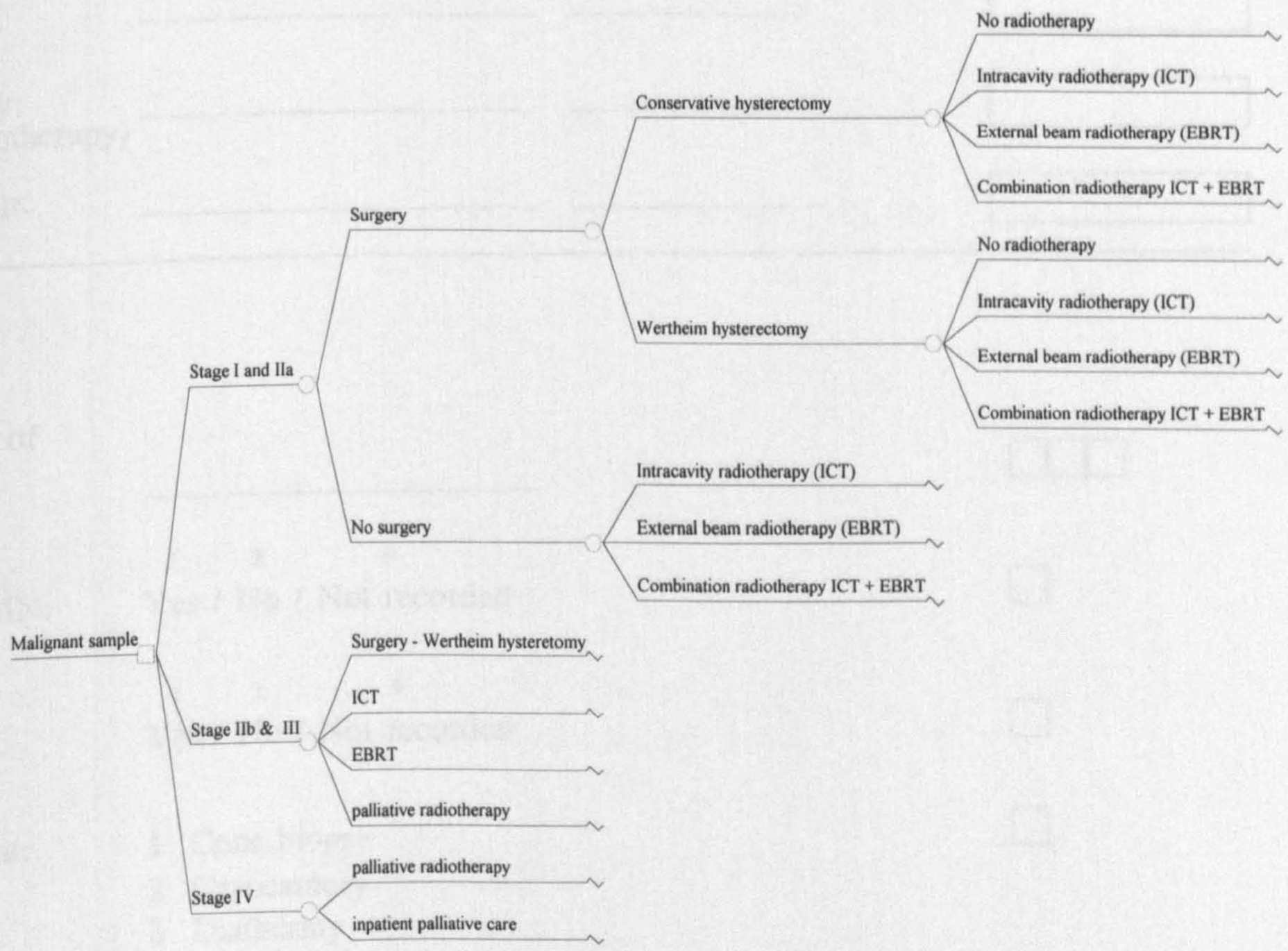
Appendix 6.1 Diagnosis/staging algorithm for cervical cancer from the literature



Treatment algorithm for breast cancer by stage from the literature.



Appendix 6.2

CANCER IN TRENT

CERVICAL CANCER ABSTRACT

DIAGNOSIS FORM

Abstracter: ☐☐

SIC INFO

Current Date: ☐☐☐☐☐☐

Study No: ☐☐☐

trict Code: ☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

ient's Name: _____

Date of Birth: ☐☐☐☐☐☐

ical Trial: 1 2 Yes/No ☐

Trial No: _____

atment

	Hospitals:	Consultants:	Hospital Number:
Diagnosis:	_____	_____	☐
Surgery:	_____	_____	☐
Radiotherapy:	_____	_____	☐
Systemic Therapy: (Hormone/Chemotherapy)	_____	_____	☐
Regular follow-up:	_____	_____	☐

STORY

uration of history of mptoms (weeks): _____ ☐☐☐

istory of CIN/CGIN: 1 Yes / 2 No / 9 Not recorded ☐

evious cervical atment: 1 Yes / 2 No / 9 Not recorded ☐

thod of treatment: ☐

1 Cone biopsy
2 Cryocautery
3 Diathermy
4 Cold coagulation
5 Laser treatment
6 Loop excision (LLETZ)
7 Other

"Other", please specify: _____

Study No: ☐☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

HISTORY (continued)

Date of treatment of pre-invasive disease: ☐☐☐☐☐☐

Reason for treatment: ☐
1 CIN 1
2 CIN 2
3 CIN 3
4 Other

If "Other", please specify: _____

Previous smear: ☐
1 2 9
Yes / No / Not recorded

Date of last normal smear: ☐☐☐☐☐☐

History of smoking: ☐
1 2 3 9
Non-smoker/Current smoker/Ex-smoker/Not recorded

If current smoker, no of cigarettes smoked per day ☐☐

If ex-smoker, no of months since stopped smoking ☐☐☐

Mode of presentation: ☐
1 Woman
2 GP
3 Screening
4 GUM Clinic
5 Other

If "Other", please specify: _____

Menopausal status: ☐
1 2 9
Pre / Post* / Not recorded
(* more than 1 year since last period)

Oophorectomy in past: ☐
1 2 9
Yes / No / Not recorded

Study No: ☐☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

DIAGNOSIS

Investigation	1 Yes 2 No 9 Not recorded	1 IP 2 OP 3 DC	Date of Investigation	Date Admitted	Date Discharged
Cytology	____ ☐	____ ☐			
Colposcopy	____ ☐	____ ☐			
Punch biopsy	____ ☐	____ ☐			
Cone biopsy	____ ☐	____ ☐			
Loop excision	____ ☐	____ ☐			
Dilatation & curettage (D & C)	____ ☐	____ ☐			
Cystoscopy	____ ☐	____ ☐			
Chest X-ray	____ ☐	____ ☐			
Intravenous pyelogram (IVP)	____ ☐	____ ☐			
Proctoscopy	____ ☐	____ ☐			
Other, please specify: _____	____ ☐	____ ☐			
Other, please specify: _____	____ ☐	____ ☐			

Date of diagnosis (d/m/y): ☐☐☐☐☐☐

Stage as recorded in notes: _____ ☐

Tumour size/volume (cm): _____ ☐☐.☐

Study No: ☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

HISTOPATHOLOGY

Histology (attach copy of path report):

Date of report (d/m/y): ☐☐☐☐☐☐

Report no:

Pathological stage: 1 2 3 4 5 6 7 8 9
Ia /Ib /IIa /IIb /IIIa /IIIb /IVa /IVb /Not recorded ☐

Grade: 1 2 3 9
Well/Moderately/Poorly differentiated/Not recorded ☐

Type: ☐
1 Carcinoma in situ only (CIN 3)
2 Adenocarcinoma in situ only
3 Squamous carcinoma
4 Adenocarcinoma
5 Adenosquamous
6 Other/Mixed
9 Not specified

If "Other/Mixed", please specify: _____

Mucin stains (positive): 1 Yes / 2 No / 9 Not recorded ☐

Pathological size (cm): _____ ☐☐.☐

Lesion type: ☐
1 Exophytic (proliferative growth at cervix with surface ulceration)
2 Infiltrative (abnormal growth directed inwards)
3 Ulcerating

Extent of tumour: ☐
1 Confined to cervix
2 Beyond cervix and involving the vagina (but not the lower third) and/or infiltrating the parametrium (but not to pelvic side wall)
3 Extension to pelvic side wall and/or lower third of vagina
4 Beyond pelvis or involving mucosa of bladder or rectum

Study No: ☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

HISTOPATHOLOGY (continued)

Excision margins clear: 1 Yes / 2 No / 8 Not applicable / 9 Not recorded ☐

Vascular invasion: 1 Yes / 2 No / 8 Not applicable / 9 Not recorded ☐

Lymphatic spread: 1 Yes / 2 No / 8 Not applicable / 9 Not recorded ☐

Lymph nodes sampled	**No sampled**	**No involved**	**No not involved**
Internal iliac	_____	_____	_____
External iliac	_____	_____	_____
Obturator fossa	_____	_____	_____
Other, please specify:			
_____	_____	_____	_____
_____	_____	_____	_____

Total number of lymph nodes obtained: ☐☐

Total number of lymph nodes involved: ☐☐

Total number of lymph nodes not involved: ☐☐

Spread to local organs: 1 Yes / 2 No / 9 Not recorded ☐

Site involved: 1 Bladder/2 Rectal/3 Other/9 Not recorded ☐

If "Other", please specify: _____

Study No: ☐☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

HISTOPATHOLOGY (continued)

Spread to distant organs: 1 Yes / 2 No / 9 Not recorded ☐

Site involved: 1 Lungs/2 Bone/3 Liver/4 Other/9 Not recorded ☐

If "Other", please specify: _____

TREATMENT

If patients require any further surgery, radiotherapy or chemotherapy, please record relevant information in comment box at end of form.

Decision to treat: ☐

1 Clinician preference
2 Patient preference
3 Patient unfit for surgery
4 Stage too advanced for surgery
5 Other

If "Other", please specify: _____

Surgery

Surgical treatment: 1 Yes / 2 No ☐

1 IP / 2 OP / 3 DC ☐

Date admitted: ☐☐☐☐☐☐

Date discharged: ☐☐☐☐☐☐

Date of surgery: ☐☐☐☐☐☐

Type of surgery: ☐

1 None
2 Conization
3 Total/Conservative abdominal hysterectomy (no pelvic lymph node dissection)
4 Radical/Wertheim's hysterectomy (pelvic lymphadenectomy)

If oophorectomy, please fill in details on page 8

Duration of operation: ☐☐hrs ☐☐mins

Study No: ☐☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

TREATMENT (continued)

Radiotherapy

Radiotherapy:

1 Not given
2 Internal (intracavitary)
3 External beam
4 Internal and external

☐

1 2
IP / OP ☐

Date started (d/m/y): ☐☐☐☐☐☐

Date finished (d/m/y): ☐☐☐☐☐☐

No of fractions: _____ ☐☐

Total dose (cGy): ☐☐☐☐

1 2
Intent of radiotherapy: Palliative/Curative ☐

Chemotherapy

1 2
Chemotherapy: Yes / No ☐

1 2
Single agent/Combination ☐

Study No: ☐☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

TREATMENT (continued)

Drugs:

1	Ifosfamide	5
2	Cisplatinum	6
3	Bleomycin	7
4	BIP (bleomycin, ifosfamide, cisplatinum)	8

Course/ Cycle	Drugs	Dose	1 2 IP / OP	Date Started	Date Finished
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		
	____ ☐		____ ☐		

Oophorectomy: 1 Bilateral / 2 Unilateral / 3 No / 4 Already done ☐

Hormone replacement therapy: 1 Yes / 2 No / 9 Not recorded ☐

Date started (d/m/y): ☐☐☐☐☐☐

Study No: ☐☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

FOLLOW UP/OUTCOME

Frequency of follow up visits in first 2 years: ☐

1 Within 3 months (<3 months)
2 Every 3-5 months
3 Every 6-11 months
4 Yearly (12+ months)

Frequency of follow up visits in following 3 years: ☐

1 Within 3 months (>3 months)
2 Every 3-5 months
3 Every 6-11 months
4 Yearly (12+ months)
5 Discharged to GP

Frequency of Investigations Per Year

Investigation	1990	1991	1992	1993	1994	1995
Outpatient check up						
Radiotherapy clinic check up						
Clinical examination of vault						
Cytologic smear						
Bimanual palpation						
Chest X-ray						
Ultrasound						
Other:						
Other:						

Date of discharge to GP (d/m/y): ☐☐☐☐☐☐

Study No: ☐☐☐

Patient's name: _____ TIHSR ID: ☐☐☐☐☐☐☐☐

COMMENTS:

Appendix 6.3 Resource use by stage – invasive cervical cancer

Event	All	Stage I (128)		Stage II (76)		Stage III (41)		Stage IV (15)	
		n	% of stage I	n	% of stage II	n	% of stage III	n	% of stage IV
Wertheims hysterectomy	78	57	45	19	25	2	5	0	0
Total hysterectomy	17	14	11	3	4	0	0	0	0
Chemotherapy	26	5	4	16	21	5	12	0	0
Primary radical radiotherapy	161	67	53	59	78	30	71	2	13
Primary Palliative radiotherapy	18	1	1	3	4	6	14	8	53
Hormone replacement therapy	56	34	27	21	28	1	2	0	0
Investigation	68	23	18	30	40	11	26	4	27
Palliative care	20	3	2	10	13	4	10	3	20
Inpatient palliative care	56	8	6	25	33	15	36	8	53

Appendix 6.4 Resource use by cancer stage years 1-7 – Invasive cervical cancer

		Patients using resources by stage (%)			
YEAR 1		**I (n=128)**	**II (n=76)**	**III (n=41)**	**IV (n=15)**
Diagnosis	Cytology	39	30	21	13
	Colposcopy	78	47	31	27
	Punch Biopsy	50	70	67	53
	Cone biopsy	52	22	17	0
	Loop excision	2	3	0	0
	D & C	54	51	50	27
	Cystoscopy	39	62	67	60
	Chest x-ray	52	53	55	80
	IVP	38	40	43	40
	Proctoscopy	0	0	5	0
	Lymphangiogram	17	12	5	7
	Ultrasound	7	11	31	47
	CT scan	24	28	26	20
	Chest x-ray	2	3	2	13
	Sigmoidoscopy	1	0	2	13
	Abdominal x-ray	1	1	0	0
	Kidney x-ray	1	0	0	0
	Pelvic x-ray	2	0	0	7
	Bone scan	0	1	2	0
	MRI	6	8	5	0
	Laparotomy	2	0	2	7
	Polypectomy	1	0	0	0
Surgery	Wertheims hysterectomy	44	24	5	0
	Conservative hysterectomy	11	3	0	0
Radiotherapy	Radical Intracavity	11	5	1	0
	Radical External beam	4	13	14	0
	Radical Internal + External	41	64	55	13
	Palliative Intracavity	0	1	0	0
	Palliative External beam	1	4	10	27
	Palliative Internal + External	0	1	5	27
Chemotherapy		0	8	5	0
Hormone replacement therapy		17	11	0	0
Investigations		6	13	17	13
Inpatient palliative care		2	9	26	53
Palliative care		0	5	5	20

		I (n=128)	II (n=76)	III (n=41)	IV (n=15)
YEAR 1					
Follow-up	Outpatient visit	56	41	14	27
	Radiotherapy clinic	40	49	57	40
	Bimanual palpation	10	16	10	7
	Bone scan	0	0	0	0
	Clinical examination	43	33	29	20
	Colposcopy	0	0	0	0
	CT scan	4	3	14	0
	Chest x-ray	7	3	17	33
	Cystoscopy	2	3	2	0
	IVP	2	0	0	7
	Liver function test	0	0	2	0
	MRI scan	2	4	5	0
	Sigmoidoscopy	0	1	2	0
	Cervical smear	27	5	2	7
	Spine x-ray	2	0	2	0
	Ultrasound	2	7	7	7
YEAR 2					
Radiotherapy	Radical Intracavity	1	0	2	0
	Radical External beam	0	0	2	0
	Radical Internal + External	0	0	0	0
	Palliative Intracavity	0	0	0	0
	Palliative External beam	0	1	0	13
	Palliative Internal + External	0	0	0	0
Chemotherapy		0	11	2	0
Hormone replacement therapy		21	21	0	0
Investigations		9	11	10	0
Inpatient palliative care		2	17	2	0
Palliative care		0	4	5	0
Follow-up	Outpatient visit	57	47	19	7
	Radiotherapy clinic	46	66	50	27
	Bimanual palpation	20	20	12	13
	Bone scan	3	4	7	0
	Clinical examination	64	54	29	13
	Colposcopy	2	0	0	0
	CT scan	6	16	12	7
	Chest x-ray	9	22	14	7
	Cystoscopy	2	1	10	0
	IVP	2	0	5	7

		I	II	III	IV
YEAR 2					
Follow up	Liver function test	1	1	0	0
	MRI scan	1	3	2	0
	Sigmoidoscopy	1	3	0	0
	Cervical smear	47	21	10	7
	Spine x-ray	2	11	0	0
	Ultrasound	4	16	7	0
YEAR 3					
Surgery	Wertheims hysterectomy	0	1	0	0
	Conservative hysterectomy	0	1	0	0
Radiotherapy	Radical Intracavity	0	0	0	0
	Radical External beam	2	2	0	0
	Radical Internal + External	0	0	0	0
	Palliative Intracavity	0	0	2	0
	Palliative External beam	2	0	0	0
	Palliative Internal + External	0	0	0	0
Chemotherapy		2	2	2	0
Hormone replacement therapy		23	21	2	0
Investigations		3	7	5	0
Inpatient palliative care		1	3	0	0
Palliative care		1	0	0	0
Follow-up	Outpatient visit	56	37	14	7
	Radiotherapy clinic	47	45	29	20
	Bimanual palpation	13	12	7	7
	Bone scan	0	4	0	0
	Clinical examination	50	29	12	7
	Colposcopy	2	0	0	0
	CT scan	5	4	7	7
	Chest x-ray	6	11	2	0
	Cystoscopy	2	1	0	0
	IVP	2	3	2	0
	Liver function test	0	0	0	0
	MRI scan	1	1	0	0
	Sigmoidoscopy	1	0	2	0
	Cervical smear	45	21	7	7
	Spine x-ray	1	3	2	0
	Ultrasound	3	8	0	0

		I	II	III	IV
YEAR 4					
Radiotherapy	Radical Intracavity	0	0	0	0
	Radical External beam	0	0	0	0
	Radical Internal + External	0	0	0	0
	Palliative Intracavity	0	0	0	0
	Palliative External beam	0	1	0	0
	Palliative Internal + External	0	0	0	0
Chemotherapy		1	3	2	0
Hormone replacement therapy		22	22	2	0
Investigations		5	4	5	13
Inpatient palliative care		1	0	7	0
Palliative care		1	0	0	0
Follow-up	Outpatient visit	46	28	12	7
	Radiotherapy clinic	41	36	14	20
	Bimanual palpation	15	12	2	13
	Bone scan	1	1	5	0
	Clinical examination	33	25	2	13
	Colposcopy	1	1	0	0
	CT scan	3	7	5	7
	Chest x-ray	7	7	5	0
	Cystoscopy	1	0	2	7
	IVP	1	0	0	0
	Liver function test	0	0	0	0
	MRI scan	1	0	0	0
	Sigmoidoscopy	2	3	2	0
	Cervical smear	34	18	5	0
	Spine x-ray	0	0	0	0
	Ultrasound	2	3	7	7
YEAR 5					
Radiotherapy	Radical Intracavity	0	0	0	0
	Radical External beam	0	1	0	0
	Radical Internal + External	0	0	0	0
	Palliative Intracavity	0	4	0	0
	Palliative External beam	1	3	0	0
	Palliative Internal + External	0	0	0	0

YEAR 5		**I**	**II**	**III**	**IV**
Chemotherapy		1	0	0	0
Hormone replacement therapy		20	22	2	0
Investigations		2	8	0	7
Inpatient palliative care		1	3	0	0
Palliative care		1	4	0	0
Follow-up	Outpatient visit	41	22	10	7
	Radiotherapy clinic	39	34	14	20
	Bimanual palpation	9	7	5	7
	Bone scan	1	3	0	0
	Clinical examination	36	24	5	7
	Colposcopy	1	0	0	0
	CT scan	5	4	0	0
	Chest x-ray	4	3	2	0
	Cystoscopy	2	0	0	0
	IVP	0	0	0	0
	Liver function test	0	0	0	0
	MRI scan	1	0	0	0
	Sigmoidoscopy	0	0	0	0
	Cervical smear	30	11	5	0
	Spine x-ray	0	1	0	0
	Ultrasound	2	1	0	0
YEAR 6					
Radiotherapy	Radical Intracavity	0	0	0	0
	Radical External beam	0	0	0	0
	Radical Internal + External	0	0	0	0
	Palliative Intracavity	0	0	0	0
	Palliative External beam	0	1	0	0
	Palliative Internal + External	0	0	0	0
Chemotherapy		0	0	0	0
Hormone replacement therapy		0	0	0	0
Investigations		0	1	0	0
Inpatient palliative care		1	0	0	0
Palliative care		0	0	0	0

		I	II	III	IV
YEAR 6					
Follow-up	Outpatient visit	38	20	5	7
	Radiotherapy clinic	31	27	15	20
	Bimanual palpation	6	7	2	0
	Bone scan	1	0	0	0
	Clinical examination	19	11	2	7
	Colposcopy	0	0	0	0
	CT scan	1	4	0	7
	Chest x-ray	2	1	0	0
	Cystoscopy	0	1	0	0
	IVP	1	3	0	0
	Liver function test	0	0	0	0
	MRI scan	0	1	0	0
	Sigmoidoscopy	0	0	0	0
	Cervical smear	18	8	0	0
	Spine x-ray	1	1	0	0
	Ultrasound	2	3	2	0
YEAR 7					
Radiotherapy	Radical Intracavity	0	0	0	0
	Radical External beam	0	0	0	0
	Radical Internal + External	0	0	0	0
	Palliative Intracavity	0	0	0	0
	Palliative External beam	0	0	0	0
	Palliative Internal + External	0	0	0	0
Chemotherapy		0	0	0	0
Hormone replacement therapy		0	0	0	0
Investigations		0	0	0	0
Inpatient palliative care		0	0	0	0
Palliative care		0	0	0	0

YEAR 7		**I**	**II**	**III**	**IV**
Follow-up	Outpatient visit	1	0	0	0
	Radiotherapy clinic	3	2	0	0
	Bimanual palpation	0	0	0	0
	Bone scan	0	0	0	0
	Clinical examination	0	0	0	0
	Colposcopy	0	0	0	0
	CT scan	0	0	0	0
	Chest x-ray	0	0	0	0
	Cystoscopy	0	0	0	0
	IVP	0	0	0	0
	Liver function test	0	0	0	0
	MRI scan	0	0	0	0
	Sigmoidoscopy	0	0	0	0
	Cervical smear	0	0	0	0
	Spine x-ray	0	0	0	0
	Ultrasound	0	0	0	0

Appendix 6.5 Resource use of pre-invasive carcinoma of the cervix

		All (141)		CIN I (15)		CIN II (31)		CIN III (95)	
		n	%	n	% of CIN I	n	% of CIN II	n	% of CIN III
Diagnosis	Smear	33	23	5	33	6	19	22	31
	Colposcopy	141	100	15	100	31	100	95	100
	Punch biopsy	78	55	10	53	24	78	44	46
Management	Loop cone biopsy	100	71	9	60	23	74	69	72
	Knife cone biopsy	23	16	-	-	2	7	21	22
	Laser biopsy	17	12	5	33	5	16	7	7
Follow up	Smear	111	79	14	93	21	68	76	80
	Second smear	11	8	1	7	1	3	9	9
	Third smear	2	1	-	-	-	-	2	2
	Colposcopy	88	63	13	87	15	48	60	63
	Biopsy	11	8	3	20	2	7	6	6

Appendix 6.6

Explanation of UK cervical cancer screening programme since the 1980s

In 1984 the DHSS produced guidelines based on the recommendations made by the Committee on Gynecological Cytology [Department of Health and Social Security: Committee on Gynecological Cytology, 1981 #200; Department of Health and Social Security: Health Services Development, 1984 #201], this stated that all sexually active women aged 20 to 65 years should be screened at five yearly intervals. In 1988 a Department circular marked the introduction of the current programme, which extended screening to all women aged between 20 and 65, with recall at least every 5 years. Some health authorities follow this process although the majority now follow the recommendations made by the Intercollegiate Working Party on Cervical Cytology Screening to screen every 3 years. The Committee on Gynecological Cytology also called for the nationally based call and recall scheme to be replaced by local schemes, using computer facilities wherever possible. In fact it is FPC's who now perform the role of call and recall with computerised systems. The potential for primary care to influence and improve coverage of target populations was recognised. Hence, the 1990 general practitioner contract set target payments for cervical cancer screening. Payments are triggered on reaching 50% or 80% coverage of the target population (women aged between 25 and 64) over the preceding 5.5 years. The 50% coverage target rate is met with a lower target payment. This has led to a considerable increase in screening activity. Coverage of the target population has increased, as can be seen in the table below [Government Statistical Service, 1989-1995 #202].

Year	England (% coverage in last 5 years)	Trent (% coverage in last 5 years)	Lowest coverage	Highest coverage
1989-1990	62%	72%	34%	79%
1990-1991	74%	83%	61%	86%
1991-1992	80%	88%	64%	88%
1992-1993	83%	89%	70%	89%
1993-1994	84%	90%	75%	90%
1994-1995	86%	91%	76%	91%

Chapter 7

Lung Cancer

7.1 Introduction

As is the case for most industrialised countries, lung cancer is the most prevalent form of cancer in the United Kingdom. Along with ischaemic heart disease, cerebrovascular disease and pneumonia, it has ranked amongst the top four causes of mortality over the past three decades[1]. The risk of lung cancer, as with most cancers, increases with age (Figure 7.1). Lung cancer is uncommon before the age of forty-five and then increases rapidly with age, peaking at the age of 70-74 years. Lung cancer is primarily a disease of the elderly with approximately 73% of lung cancer registrations in Trent occurring amongst the over 65's. It is also predominantly a male disease with the ratio of male to female lung cancer patients at approximately 2:1. Recently, there has been a decline in the incidence in men, but the numbers of women with lung cancer are still rising. These trends are shown for the Trent data in Figure 7.2. The increasing incidence and mortality in women is believed to reflect the uptake of cigarette smoking in women a couple of decades later than men. The vast majority of lung cancer cases (about 9 out of 10) are caused by tobacco smoking[2]. Although smoking is by far the major cause of lung cancer, it is not the only cause. Exposure to certain carcinogens in the workplace or at home, such as asbestos and radon, also increase the risk of lung cancer.

Along with great morbidity, lung cancer is also associated with high mortality rates, in fact with the 5-year survival rates being so poor (7% survival at 5 years[2]) and there being a short clinical course and poor prognosis it is unsurprising to find that mortality rates are a good approximation for the incidence of the disease and vice versa.

Although it is generally believed that lung cancer treatment places a substantial burden on national health care resources, few data are available to substantiate this belief[3]. This chapter presents estimates of the direct economic costs of the hospital treatment of lung cancer, based on the records of a sample of patients drawn from the Trent region.

From the most recent registration and mortality figures, lung cancer is responsible for:

- 37,312 new registrations in England and Wales in 1992, of which male registrations accounted for 24,985, and female registrations accounted for 12,327[4].
- 3,177 new registrations in the Trent region in 1997, (males 2,114, females 1,063)[5].
- The incidence of male lung cancer in England and Wales over the past decade is declining, while the incidence of female lung cancer is increasing. These trends are similar in the Trent region (see Figure 7.2).
- 30,199 deaths from lung cancer in England and Wales in 1998, (males 19,036, females 11,163)[6].
- 2,893 deaths in Trent in 1997 (males 1,915, females 978)[5].
- Internationally England and Wales is ranked twelfth worst out of 22 countries for lung cancer mortality rates. Scotland has the highest death rate from lung cancer, 63 per 100,000 population, England and Wales has a death rate of 43 per 100,000 population, and Japan has the lowest at 21 per 100,000 population[7].
- The 5-year relative survival rate for lung cancer in England and Wales is poor at approximately 7%[8].
- 57 million years of life were lost due to lung cancer in 1992[7].

Figure 7.1 Number and age- and gender-specific lung cancer registrations, Trent 1994

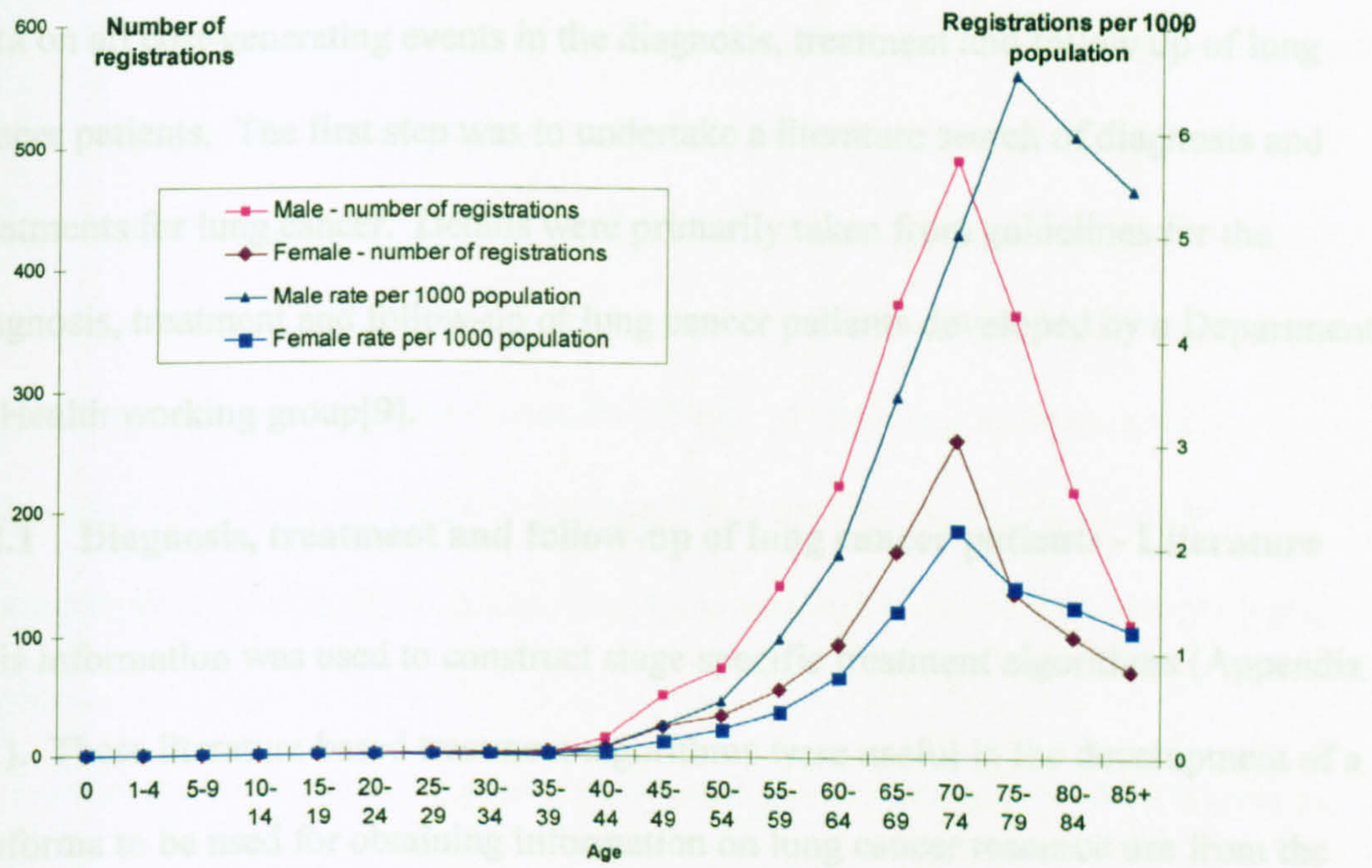
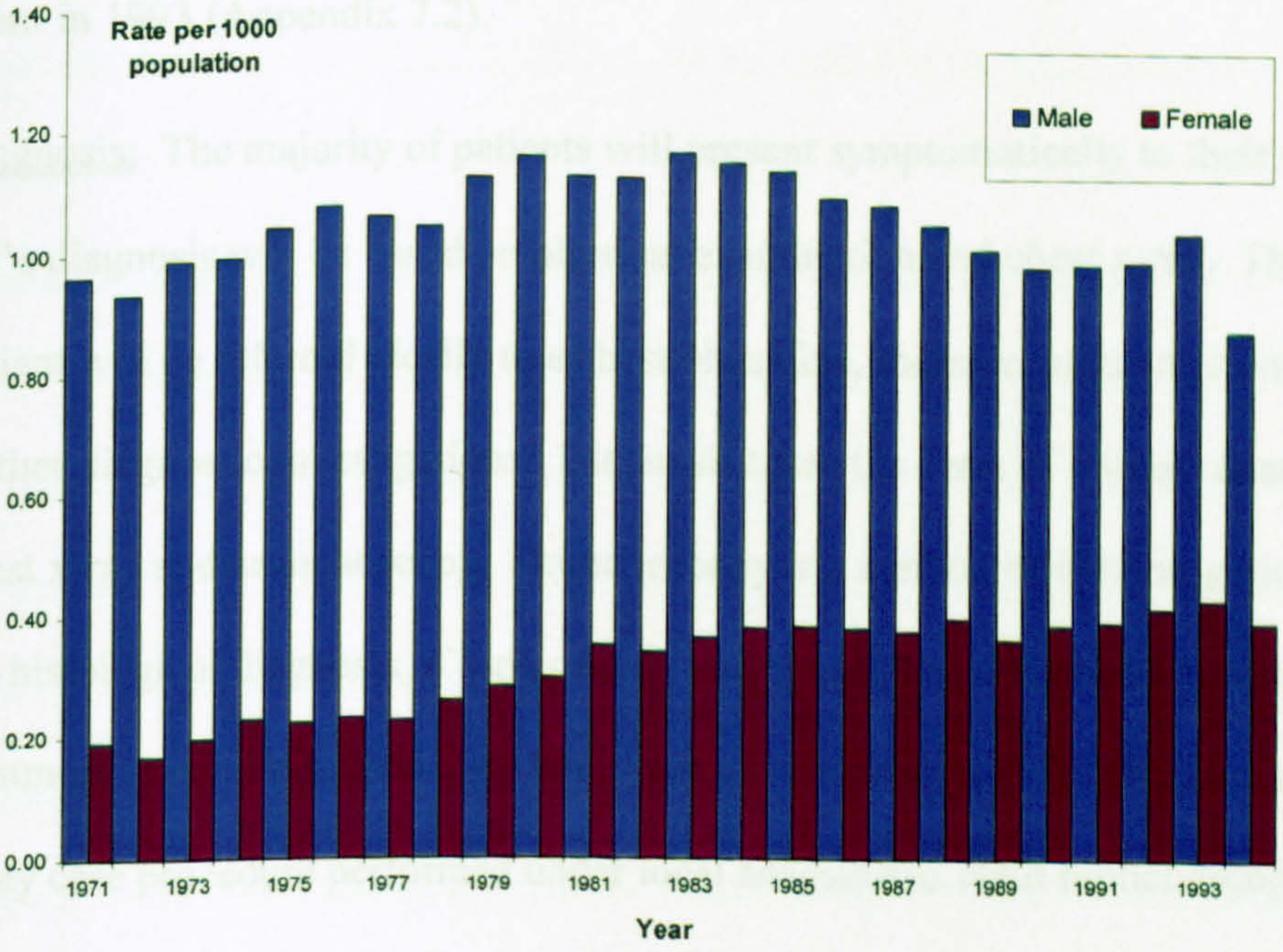


Figure 7.2 Male and female lung cancer registrations, 1971-1994 Trent (rate per 1000 male and female population)



7.2.1 Methods

The assessment of the resource use and cost implications of lung cancer care requires data on all cost-generating events in the diagnosis, treatment and follow up of lung cancer patients. The first step was to undertake a literature search of diagnosis and treatments for lung cancer. Details were primarily taken from guidelines for the diagnosis, treatment and follow-up of lung cancer patients developed by a Department of Health working group[9].

7.2.1 Diagnosis, treatment and follow-up of lung cancer patients - Literature

This information was used to construct stage specific treatment algorithms (Appendix 7.1). These literature based treatment algorithms were useful in the development of a proforma to be used for obtaining information on lung cancer resource use from the medical notes of a ten per cent sample of those patients diagnosed with lung cancer in Trent in 1993 (Appendix 7.2).

<u>Diagnosis:</u> The majority of patients will present symptomatically to their GP. The GP's diagnosis will be based on physical examination and chest x-ray. The suspicious patient will be referred ideally to a chest physician, thoracic surgeon or oncologist for further diagnostic investigations. Diagnosis takes the form of clinical examination, chest x-ray and bronchoscopy. Bronchoscopy is a method of obtaining biopsies for the histological diagnosis of lung cancer, and should be performed whenever active treatment is required. There are two types of bronchoscopy; flexible bronchoscopy is a day case procedure performed under local anaesthetic, rigid bronchoscopy is a more complicated operation and is required if there are difficulties with the former

procedure or if larger specimens are required. Percutaneous needle biopsy is necessary if a sample is taken from the periphery of the lung.

Other procedures commonly performed at this stage include lung function tests to assess the patients' ventilatory capacity and radioisotope scanning, e.g. bone, liver and brain scans which are useful in confirming clinical suspicion and improving the detection of stage. CT scanning is particularly beneficial in identifying peripheral tumours and can aid percutaneous needle biopsy. The CT scan has generally superseded older invasive surgical investigations such as mediastinoscopy and mediastinotomy which allowed sampling and visualisation of the mediastinal lymph nodes.

For decisions about clinical management and for the purpose of constructing the treatment algorithm, lung cancer patients are differentiated according to cell type. The major histologic distinction is between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC can be split further into limited and extensive disease.

Treatment NSCLC: The majority of lung cancer patients (typically around 75-80 per cent) are diagnosed with non-small cell lung cancer (NSCLC)[10]. For them, surgical techniques may prove appropriate, whilst inoperable patients will be treated with radiotherapy[11] and, rarely in the UK at present, chemotherapy. The major chance of cure for this group of patients is provided by surgery, although only 20% of patients are deemed to be acceptable for surgical treatment. If there are no contraindications to surgery in the initial patient assessment these patients are then subjected to thoracic CT scanning to assess the spread to the mediastinum. If there is no tumour spread

then the patient should be considered for thoracotomy without any further investigations. If there are signs of spread to the mediastinum then the patient will have to undergo further preoperative investigations in the form of mediastinoscopy and/or mediastinotomy. Surgical resection of the lung is in the form of either pneumonectomy (removal of the whole lung) or lobectomy (removal of part or a wedge of the lung). 5% of the patients who undergo thoracotomy will subsequently be found to be unsuitable for resection, and will therefore follow the treatment pathway of the inoperable patients.

Inoperable patients are either treated with radiotherapy or palliatively with a mixture of symptom control, palliative radiotherapy and/or palliative chemotherapy. Radiotherapy with the intention of cure is given to those patients who are unsuitable for surgery but whose disease is confined to the chest. The total dose of radiotherapy ranges from 50-60 Gy delivered with megavoltage equipment (linear accelerator or cobalt-60) over 3-6 weeks. 5-year survival is approximately 28%.

Treatment SCLC: Chemotherapy is the preferred treatment for the small cell lung (SCLC) cancer cases, on occasions in combination with radiotherapy[9]. Median survival for untreated limited SCLC is only 14 weeks, 7 weeks for extensive disease. Chemotherapy improves this median survival significantly to 12-18 months for limited disease and 9 months for extensive disease. Radiotherapy may be given in some cases after chemotherapy to enhance tumour control. For those patients with poor performance status the main aim of treatment is palliation using the minimum of cytotoxic drugs to control the disease and maintain a reasonable quality of life.

Follow up: Patients will usually receive post-treatment follow-up involving x-rays and/or scanning, although practices and policies appear to vary widely between clinics[12, 13]. The most common investigations include chest x-ray, bone and brain scans and CT scanning.

The majority of patients will eventually require palliative chemotherapy, palliative radiotherapy and/or symptom control. This having been said, it is probable that many patients never receive any treatment for lung cancer.

7.2.2 Estimation of treatment costs

The ideal method for costing any disease process is to have resource use and cost information on a patient specific basis. Given that the epidemiology of cancer in the UK has long been documented by the Cancer Registries on such a patient specific basis, it might be thought that a population-based resource use audit could be easily accomplished using pre-collected data. However, the Registry databases do not usually include details of either resource use or cancer stage at diagnosis. The cost estimates were therefore based on an analysis of treatment records of a sample of individual patients. Individual patient costing provides far more realistic overall cost estimates than does average costing or simulated costing. However, by auditing cost events for each single patient, the procedure is particularly time-consuming[14]. With 2,900 lung cancer cases being diagnosed annually in Trent in 1993, a complete cost analysis of a full year's cohort was deemed to be prohibitively expensive.

Accordingly, a 10 per cent random sample, amounting to 290 cancer patients from the Trent register was identified for four districts where primary treatment was undertaken (North Lincolnshire, Nottinghamshire, Rotherham and Sheffield). All had been

nominally diagnosed with lung cancer in 1993. This particular year was selected as a baseline on the grounds that it would permit the construction of a resource audit for each patient for up to four years, a period following diagnosis during which the majority of cancer recurrences and treatment complications would be likely to occur. If the patient was still alive after four years s/he was assumed to be cured and return to the life expectancy of the normal population[9]. The costing exercise was based on a retrospective examination of the medical case notes of the patient sample. This was facilitated by the use of a proforma developed with the aid of information obtained from the initial literature review on diagnosis and treatment and designed to collect both the epidemiological and economic data (see Appendix 7.2). It was verified by a consultant thoracic surgeon based at the Queen's Medical Centre, Nottingham, and piloted on 30 medical notes of lung cancer patients treated at the same hospital.

An attempt to retrieve the full treatment records for all 290 cases revealed that, for 47, notes were untraceable, or cancers had been misclassified, either by diagnosis or by year. The initial sample according to the cancer registry had 252 patients classified as having NSCLC and 38 classified as having SCLC, however it was found that some of the patients had been misclassified by cell type. One patient was reported as being of non-small cell type, when in fact according to their medical notes the cell type was small-cell. Nine patients were reported by the registry as being small-cell lung cancer patients, where according to their medical notes they were reported as having non-small cell lung cancer. This resulted in a sample with 260 NSCLC patients and 30 SCLC patients. From this sample, further exclusions had to be made on the grounds of records being untraceable or containing no information, and cases

being misclassified by year of diagnosis (see Table 7.1). After these exclusions, 253 records were available for analysis with 227 NSCLC patients and 26 SCLC patients. For the NSCLC patients it is possible to stage the disease according to the standard TNM classification ranging from stage I to IV[15], however there was no information in the medical notes to enable this to be undertaken. For the SCLC patients, 17 were classified as having limited disease, 6 as having extensive disease and 3 patients could not be classified.

A full audit of resource-using hospital events was compiled for each of these patients, for four years following initial diagnosis or until death, if occurring earlier. The unit costs of these events were obtained from a survey of eleven of the region's principal service providers, each of whom was sent a form requesting the cost of the various activities, as performed at their site (Table 7.2). Since 1993, all National Health Service (NHS) providers have been required to follow a uniform accounting protocol, requiring that their services be costed at full cost, i.e. all service-specific variable costs, with the inclusion of the relevant components of fixed and overhead costs[16]. I employed the mean of the reported costs of each event in the estimates, converted back to 1993 prices using the NHS pay and price index[17]. By combining the unit cost estimates with the resource use information, the mean costs of diagnosis, treatment and follow up by cell type at diagnosis for the sample over the follow up period were obtained. Given that management events were occurring across time, the costs of events occurring in years 2 through 4 following diagnosis were discounted at 6 per cent. In other words, mean four-year costs were expressed as a 1993 present value, to represent the prospective cost implications from the perspective of the

baseline year. The discount rate chosen was that conventionally employed in evaluations of UK public sector projects[18].

Table 7.1 Lung cancer sample: retrieval of case notes and exclusion of patients (by district of primary treatment)

	North Lincolnshire	Nottinghamshire	Rotherham	Sheffield
SCLC				
Total sample size	5	3	5	17
No diagnosis of lung cancer	-	-	-	1
Missing notes	-	-	-	2
Diagnosed outside 1993	-	-	-	1
NSCLC				
Total sample size	66	71	60	63
No diagnosis of lung cancer	2	-	1	1
Missing notes	5	1	7	2
No information in notes	2	-	-	-
Diagnosed outside 1993	4	2	4	2

Table 7.2 Unit costs of diagnosis, treatment and follow up events (£ UK 1993)

Investigation/Treatment	Unit cost in 1993 prices
Chest x-ray	11.51
Ultrasound	27.91
CT scan	94.33
Other x-ray	21.38
Bone scan	77.01
Bronchoscopy	308.36
Percutaneous needle biopsy	67.93
Mediastinoscopy (per day)	239.46
Sputum cytology	13.67
FNA	43.11
Lung function test	79.82
Biopsy	42.29
Liver function test	6.57
MRI scan	163.64
Blood count	3.31
ECG	2.84
Outpatient visit	52.40
biochemistry	6.25
haemotology	6.57
microbiology	7.91
Surgery/Thoracotomy (per day)	382.13
Inpatient palliative care (per day)	231.54
Inpatient stay (general-per day)	186.17

Table 7.2 continued.

Radiotherapy Costs 1993 Prices (£ UK)

Radiotherapy Type	Cost per attendance (£)	Cost per episode (£)
Low energy:	77.22	
1-4 fractions		290.70
5-10 fractions		726.76
Simple:	81.76	
1-4 fractions		817.60
5-10 fractions		2434.64
11-15 fractions		4378.72
16-25 fractions		6649.85

Chemotherapy Costs 1993 Prices (£ UK)

Cytotoxic Drug	Dosage	Cost (£)
Etoposide	50 mg (20 tablets)	113.95
	100 mg (10 tablets)	99.57
Cyclophosphamide	50 mg (20 tablets)	1.91
Vincristine	1 ml	9.80
	2ml	19.00
	5 ml	39.60
Cisplatin	10ml/10mg	5.15
	50ml	25.73
	100ml	51.54
Ifosfamide	500mg	7.75
	1g	13.50
Methotrexate	1ml	1.94
	2ml	2.69
	4ml	5.14
	8ml	10.28
	20ml	25.71
	40ml	45.71
	200ml	205.71
Mitomycin	2mg	6.32
	10mg	20.80
	20mg	39.67

7.3 Results

7.3.1 Sample characteristics

The sample characteristics by cell type are displayed in Tables 7.3 and 7.4. Ninety per cent of the sample are classified as NSCLC with the remaining ten per cent as SCLC. Seventy-one per cent of the NSCLC are cancers found in the male population sample, while sixty-nine per cent of the SCLC are found in men. The mean/median age at diagnosis of the samples of patients was 71/72 years (SD 9 and range 35 years) for NSCLC and 66/67 years (SD 9 and range 47 years) for SCLC. Only six per cent of the NSCLC and four per cent of the SCLC patients were alive at the time of data collection. This corresponds with national 5-year survival rate of 7%[2]. Given that the greatest risk factor for lung cancer is cigarette smoking. It is interesting to note that ninety and ninety-two per cent of the NSCLC and SCLC sample respectively are smokers or ex-smokers.

Table 7.3 Sample characteristics

Cell Type	No (%)	Mean age at diagnosis (s.d.)	No. deceased at abstraction (%)	No. alive at abstraction (%)
NSCLC	227 (90%)	71 (9.34)	214 (94%)	13 (6%)
SCLC	26 (10%)	66 (9.21)	25 (96%)	1 (4%)

Table 7.4 Gender and smoking history by cell type

Cell Type	Gender No. (%)		Smoking history No. (%)			
	Male	Female	Smoker	Non-smoker	Ex-smoker	Not recorded
NSCLC	162 (71%)	65 (29%)	97 (43%)	11 (5%)	106 (47%)	12 (5%)
SCLC	18 (69%)	8 (31%)	12 (46%)	2 (8%)	12 (46%)	-

Table 7.5 explores the mode of presentation of the patients in the sample. The majority (61%) presented at a GP surgery due to symptoms, such as coughing up blood or difficulty breathing. The remainder was detected by routine chest x-ray or investigations for other diseases, or by other routes such as presenting in accident and emergency departments.

Table 7.5 Mode of presentation of lung cancer patients by cell type

Cell Type	GP due to Symptoms	Routine CXR	Investigation for other disease	Other
NSCLC	141 (62%)	10 (4%)	12 (5%)	64 (28%)
SCLC	13 (50%)	2 (8%)	4 (15%)	7 (27%)

7.3.2 Resource use

Considerable diversity with respect to cost-events was evident on a patient-by-patient basis. For example, a total of 19 distinct diagnostic events were found to have occurred amongst the sample as a whole, and in a wide variety of combinations. In most cases, many or all of the diagnostic events were undertaken on an in-patient basis although, in others, some of the tests were administered on an out-patient or day-case basis, with differential consequences for costs. Appendix 7.3 displays data on the frequency of use of investigations and treatments by year in which it was incurred. Surgery included thoracotomy, lobectomy, segmentectomy and pneumonectomy. Patient-specific radiotherapy costs varied with type (palliative or radical, low energy or simple), number of fractions and setting (e.g. in-patient or out-patient). Within the sample, 7 different chemotherapy drugs were employed, in combinations, dosages and

settings specific to each of the patients so treated. Post-primary treatment, each patient received one or more of up to 13 forms of immediate procedure or follow-up investigation, largely the same as those used as initial investigations. Twenty per cent of NSCLC, and 23% of SCLC, patients required further inpatient stays, including emergency admission, surveillance for metastases, spinal cord compression, pleural effusion and blood transfusion. One of the most significant factors contributing to the cost of cancer care is the cost of hospitalisation. Table 7.6 displays data pertaining to usage of inpatient care over the entire four-year period. Costs associated with in-patient episodes accounted for 80 and 76 per cent of total mean costs, for NSCLC and SCLC, respectively.

Table 7.6 Inpatient length of stay by cell type

	NSCLC (227)				SCLC (26)			
	Patients receiveing: No.	%	Mean LOS	SD	Patients receiveing: No.	%	Mean LOS	SD
Diagnosis	168	74%	13.1	15.0	20	77%	11.2	8.6
Surgery	17	7%	13.7	6.3	-	-	-	-
Chemotherapy	3	1%	4.0	2.0	5	19%	15.4	9.2
Primary Radical radiotherapy	3	1%	14.7	9.1	-	-	-	-
Primary Palliative radiotherapy	18	8%	13.2	16.8	-	-	-	-
Investigation 1	44	19%	12.5	12.9	6	23%	6.3	5.6
Investigation 2	16	7%	7.9	5.5	3	12%	5.3	5.8
Investigation 3	3	1%	6.3	4.0	3	12%	10	11.3
Investigation 4	1	1%	2.0	-	-	-	-	-
Further investigations	44	19%	12.5	12.9	6	23%	6.3	5.6
Inpatient palliative care	104	46%	25.1	48.3	11	42%	13.7	11.3

n = number of patients by stage experiencing inpatient stays
% = percentage of patients by stage experiencing inpatient stays
Mean LOS = the average length of stay in days

7.3.2 Treatment costs

Table 7.7 displays the mean four-year costs by broad management category. Only 14 patients (6 per cent) survived the full four years following diagnosis and, on average, 96 and 97 per cent of all costs were incurred in the first year in the two sub-samples, respectively. In consequence, the cost estimates were extremely insensitive to variations in the discount rate (table 7.8). It is evident from Table 7.7 that differences in the mean costs of the two lung cancer types were insignificant (mean difference in cost = £481.94, t-test; t = 0.328, $P = 0.743$). The costs associated with diagnosis and inpatient palliative care accounted for the greatest proportion of total care costs (approximately 50 per cent and 18-26 per cent respectively across the two cell types).

Exploring the cost data in detail the reported skew for the non-small cell cancer type was high at 4.86, a histogram plot of the data verified the skew and highlighted one patient outlier whose total cost of care exceeded £75,000, excluding this patient from the sample resulted in a reduced mean cost for non-small cell lung cancer care of £5,832 (SD 5,559), the skew in the data was also reduced to 1.66.

Table 7.7 Four-year costs of diagnosis, treatment and follow-up by cell type, (£, 1993)

	Non-small cell lung cancer			Small-cell lung cancer		
	Mean cost	SD	% of total cost	Mean cost	SD	% of total cost
Diagnosis	2,940	3,468	47.8%	2,746	2,352	48.4%
Surgery	369	1477	6.0%	-	-	
Radical radiotherapy	191	1297	3.1%	41	192	0.7%
Palliative radiotherapy	250	814	4.1%	171	249	3.0%
Chemotherapy	17	156	0.3%	899	1,828	15.9%
Investigations	573	1639	9.3%	523	1,442	9.2%
Inpatient palliative care	1623	5519	26.4%	1,019	1,854	
Follow up	187	332	3.0%	271	360	
Total cost	6,150	7,333		5,668	4,426	
95% CI	5,191-7,110			3,881-7,456		

Table 7.8 Impact of different rates of discount on the results

	NSCLC		SCLC	
	Mean	95% CI	Mean	95% CI
Discount rate 6% (baseline)	6,150	5,191 - 7,110	5,669	3,881 - 7,456
0%	6,185	5,221 - 7,149	5,689	3,890 - 7,488
3%	6,167	5,206 - 7,128	5,679	3,885 - 7,472
9%	6,135	5,278 - 7,092	5,659	3,876 - 7,442

7.4 Impact of costs with respect to Trent region

A total of 3,482 cancers of the lung were registered as being diagnosed in the Trent region in 1993, male cancers accounted for 2,435 of this total, with the remainder, 1,047, being diagnosed in the female population. Assuming the full population of lung cancers in Trent were to present according to the proportions of each cell type identified in the Trent sample (90% NSCLC, 10% SCLC), the total discounted four-year cost of the management of lung cancer in Trent in 1993 would amount to approximately £21.3 million (£19.3 million for NSCLC and £2 million for SCLC).

7.5 Comparisons with other lung cancer costing studies

The results of this analysis on the costs of lung cancer can be compared with those of other studies (Table 7.9). To date, the most ambitious attempt to cost lung cancer management has taken place in Canada[3, 19-22]. This research produced five-year cost estimates of £10-16,000 for NSCLC and of £16-20,000 for SCLC (converted to UK £, sterling 1993, using the exchange rate and the NHS pay and price index). These estimates are considerably higher than those identified for the Trent sample, although the transparency of the Canadian research allows the identification of the sources of the discrepancies. First, the assumed per diem cost of in-patient stay was almost twice as high in the Canadian study as it was in the Trent analysis. This presumably reflects on the differential financial structures of the two health care systems and, as noted above, in-patient costs are a major component of overall management costs. Second, the methodology of the studies differs. The Canadian estimates have not been obtained solely from direct observation of patient experiences.

They are based on simulations or models of events, derived both from agreed clinical protocols and from specialist opinion on the nature of "proper practice". In particular, the Canadian protocols appeared to have allowed for more radical treatments than was observed in my sample and the authors accepted that such an assumption might have been unrealistic in the case of elderly, frail patients. For example, over 85 per cent of Canadian NSCLC patients were deemed eligible for surgical resection, with an average hospital stay of 20 days. In the Trent sample, only 8 per cent of NSCLC patients received resection, with an average stay of 14 days. Third, the Canadian study reported five-year survival following diagnosis of all forms of lung cancer at 13 per cent, superior to the observed four-year rate for Trent. The proportion of cost incurred by the Canadian patients in the first year was 82% and 83% for NSCLC and SCLC, respectively. These results are consistent with the view that the Trent patients received less aggressive therapy than was assumed to be the case for the Canadian patients.

Studies conducted in the US using Medicare charges result in significantly higher cost estimates than those reported in this thesis[23, 24]. Similar differences were found when comparing cost estimates for the breast and cervical sample based on the Trent data in chapters 5 and 6 with estimates from US studies. A German study also reported higher cost estimates for SCLC (£9,700) and NSCLC (£9,100)[25], however these results were based on a review of the medical notes for only 26 patients. Significantly higher cost estimates for small-cell-lung cancer were also reported by both an Australian (£7,900 (1993 prices)[26] and a UK based study (£10,252 (1993 prices)[27]. The major contributing cost for SCLC in both studies

were found to be due to inpatient stays and chemotherapy, accounting for 49 per cent of the total cost in the UK based study. Unfortunately, the transparency of the methods reported in each paper preclude a full investigation of why the Trent cost estimates for SCLC were significantly lower than their cost estimates[7.1].

The closest estimate to the Trent sample is based on a retrospective review of 196 patients treated for lung cancer in Southampton in 1990. Sanderson and colleagues (1992) report an average cost per lung cancer patient of £5,228 (updated to 1993 prices), however the lack of transparency in the reported methods makes a direct comparison impossible.

[7.1] The UK based study was a published conference abstract. I was unable to access their data as their work was undertaken as part of a consultancy project.

Table 7.9 Studies estimating lung cancer costs

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK, £ 1993
Evans 1993[19]	Canada	Literature review and patient data query of the National Cancer Institute (NCI) guidelines	Fees charged by Ontario Health Insurance Plans, hospitalisation and clinic visits based on previous work[28]	Canadian $	1984	Metastatic NSCLC (1st year costs)	$9,158	£7,698
Baker et al. 1991[23]	US	Retrospective review of Medicare beneficiaries from 1974-81	Medicare charges	US $	1984	Lung cancer	$12,510	£12,181
Coy et al. 1992[29, 30]	Canada	Retrospective review of records at clinic	Staff costs estimated by dividing workload by patient throughput, using salaries, actual costs of equipment and operating costs, hotel charges on inpatient stays and cost of drugs from the pharmacy department	Canadian $	1989/90	Chemotherapy Radiotherapy Assessment	$4,600-8,600 $1,650-5,890 $460-480	£2,701-5,049 £969-3,458 £270-282

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK, £ 1993
Evans et al. 1995[3, 20-22]	Canada	Investigations and their frequency from panel of lung cancer specialists at Ottowa Regional Cancer Center, treatment from the patient data query of the NCI guidelines and questionnaire responses on practice patterns by all Canadian academic thoracic surgeons (25) & 48 radiotherapists. Length of stay for diagnosis, radiotherapy and surgery fro NSCLC from Ontario cancer registry, hospitalisations and outpatient utilisation for chemotherapy, treatment of SCLC and best supportive care from previous studies[28, 31]	Fees charged by Ontario Health Insurance Plan for surgery, investigations, and physician time. Hospital cost for surgery, used per diem cost from Statistics Canada. Hospital costs for non-surgical care from previous studies[28, 31, 32]	Candaian $	1988	NSCLC:		
						Stage I	$21,400	£14,312
						Stage II	$23,881	£15,971
						Stage IIIa	$22,131	£14,800
						Stage IIIb	$19,366	£12,951
						Stage IV	$16,501	£10,901
						All stages	$19,781	£13,229
						SCLC:		
						Extensive disease	$23,789	£15,909
						Limited disease	$29,864	£19,972
						All	$25,988	£17,380

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK, £ 1993
Rosenthal et al. 1992[26]	Australia	Retrospective review of medical notes of 31 SCLC patients	Diagnostic and investigation costs based on Australian Medicare charges, inpatient stay based on New south Wales Department of Health formula, radiotherapy based on wages of staff involved and the equivalent annual cost of the equipment, chemotherapy costs included purchase price of drugs, consumables and infrastructure.	Australian $	1990	SCLC: Limited Extensive All	 $18,234 $13,177 $14,413	 £9,986 £7,216 £7,893
Sanderson et al. 1992 [33]	UK	Literature review and retrospective review of 196 patients treated for lung cancer in 1990	Hospital costs from finance department at Southampton General Hospital	UK £	Not stated	All (assume base year =1992)	£4,730	£5,228

Study	Country	Sample size and resource use data source	Source of unit cost data	Currency	Price year	Stage	Cost	UK, £ 1993
Riley et al. 1995[24]	US	Tumour registry data from SEER linked to Medicare payments	Average Medicare fees schedule	US $	Not stated	All (assume 1995 = base year)	$29,184	£12,200
Oliver et al. 2000[27]	UK	4-year retrospective review of the medical notes of 109 patients with SCLC from 1994-1997. Used focus group to clarify patient pathways	Finance department of Newcastle NHS Trust and the BNF	UK £	Not stated	SCLC: Assume 2000 base year		
						Referral and diagnosis	£2,020	£1,792
						Active therapy	£6,127	5,435
						Re-treatment	£1,620	£1,437
						Follow up	£504	£4,441
						Terminal care	£3,399	£447
						Total	£11,557	£10,252
Porzsolt F et al. 2000[25]	Germany	Retrospective review of the medical notes of 26 patients	Social insurance charges and payments made by patients	Euro	Not stated	Assume 2000 base year		
						SCLC	17,800	£9,763
						NSCLC	16,676	£9,146

7.6 Conclusions related to lung cancer costs

Detailed information on the costs of a disease such as cancer is generally not available. This is because of the enormity of the task involved in collecting and analysing the data. Cancer is a disease that occurs over extended periods of time and costs should ideally be monitored from the date of diagnosis to the date of death. Due to the poor survival rates associated with lung cancer this makes the task of estimating the costs of lung cancer management somewhat easier than those of breast cancer, which has a better prognosis and a higher chance of recurrence up to 20 years following diagnosis. Therefore, surprisingly, compared with breast cancer, relatively few costing studies in the field of lung cancer have been published. Lung cancer is always blamed for its huge burden on the public purse, but as to what these cost burdens actually are and where the major components of these costs lie have been relatively unknown and usually guessed at using 'back-of-the-envelope' calculations. The aim of this chapter was to estimate the lung cancer treatment costs and to find out for what treatment regimes the major burden of these costs lie. A detailed patient-by-patient costing analysis, based on case records for 253 patients diagnosed in 1993, revealed that the mean four-year diagnosis and management costs amounted to £6,150 and £5,668 for non-small cell and small cell lung cancer, respectively. These costs are lower than those identified in Canadian studies, the difference being explained by the use of a simulated costing methodology in these studies, lower unit costs and less aggressive interventions. But how might this information be of help to any decision maker or planner? Apart from being able to estimate the total burden of

lung cancer in cost terms for a region or Nation, the results could be used by analysts wanting to explore the cost-effectiveness of possible smoking cessation programmes or even the impact of introducing a screening programme for lung cancer. At the start of this cost analysis, it was apparent from the literature that screening for lung cancer was unlikely to be ever introduced, however this assumption was not based on any evidence. Recently there has been a revived interest in lung cancer screening, and a recent 'News' article in the British Medical Journal has highlighted a plan for a proposed screening trial for lung cancer using low radiation dose computer tomography in smokers and ex-smokers[34]. The cost analysis reported in this chapter could accordingly be used to in a pre-trial modelling exercise of the cost-effectiveness of such a screening programme to inform the trial of the important parameters in the trial, i.e. those in the model having the greatest impact on the cost-effectiveness results.

7.7 Cost comparison between the three cancer sites

Chapters 5-7 have reported on the results from the empirical estimation of the cost of breast, cervical and lung cancer in Trent region. The comparison of the cervical cancer management costs with those of breast cancer clearly indicates not only that the former are significantly higher but that the implications of stage progression for management costs differ between cancer sites. Broadly speaking, for cervical cancer, a cost plateau is reached after stage I and inter-stage cost variations thereafter are insubstantial ($F = 90.06$, $P < 0.000$, Duncans post hoc test at 5% suggests stage I costs significantly differ from stages II-IV) (see figure 7.3).

For breast cancer, the cost plateau occurs across the first three stages and costs subsequently rise at stage IV (F = 2.3, $P = 0.077$, Duncans post hoc test at 5% suggests stage IV costs significantly differ from stages I-III) (see figure 7.4). In consequence, shifting detection of disease to the earliest invasive stage exerts a greater relative impact on overall management costs for cervical cancer than it does on those for breast cancer. For cervical cancer the treatment cost economies for stage I cancers are as a result of a higher proportion of stage II-IV patients undergoing high cost inpatient radiotherapy and palliative care compared with the stage I patients. Whereas the cost driver for breast cancer patients is in terms of the significantly higher inpatient length of stay for stage IV cancer patients compared to stage I-III cancers.

An additional comparison can be made with results from a study of the cost of treating colorectal cancer, conducted in the context of the UK colorectal screening trial using faecal occult blood tests[35]. This analysis audited 360 patients over 3 years. In common with breast and cervical cancer, colorectal cancer possesses a defined staging structure, A through D, which might be considered analogous to the four stages of breast and cervical cancer. In the colorectal study, stage A cancer was found to be significantly cheaper to treat than stages B and C and, in this respect, the cost profile by stage of colorectal cancer differs from that discovered for breast and cervical cancer. In the case of colorectal cancer, however, the lower cost of stage A was largely accounted for by the potential for using low-cost surgical techniques entailing reduced lengths of hospital stay. Stage D colorectal cancer was found to be significantly cheaper to treat than the

intermediate stages, owing to shorter survival times (requiring less follow-up) and the more frequent use of relatively cheap palliative therapies (see figure 7.5). Possibly of greatest significance, however, is the colorectal study's conclusion that no sizeable treatment cost economies could be anticipated as a result of an early detection programme, a finding consistent with the breast cancer results, yet inconsistent with the cervical cancer results.

The 4-year lung cancer cost results (£6,500 - £7,100 UK, 2000 prices) (figure 7.6) can be compared directly with the 4-year breast cancer (£4,700 - £8,400 UK, 2000 prices) and the 5-year cervical cancer cost results (£9,200 - £16,100 UK, 2000 prices). For all three cancer sites the preponderance of resource use occurred in the year immediately following diagnosis.

In all four cancer sites the standard deviations of the mean costs emerged as particularly high, indicating the wide variation in patient-specific resource use even within a given stage at diagnosis.

Figure 7.3 Cost by stage for cervical cancer patients (UK £, 2000)

Figure 7.4 Cost by stage for breast cancer patients (UK £, 2000)

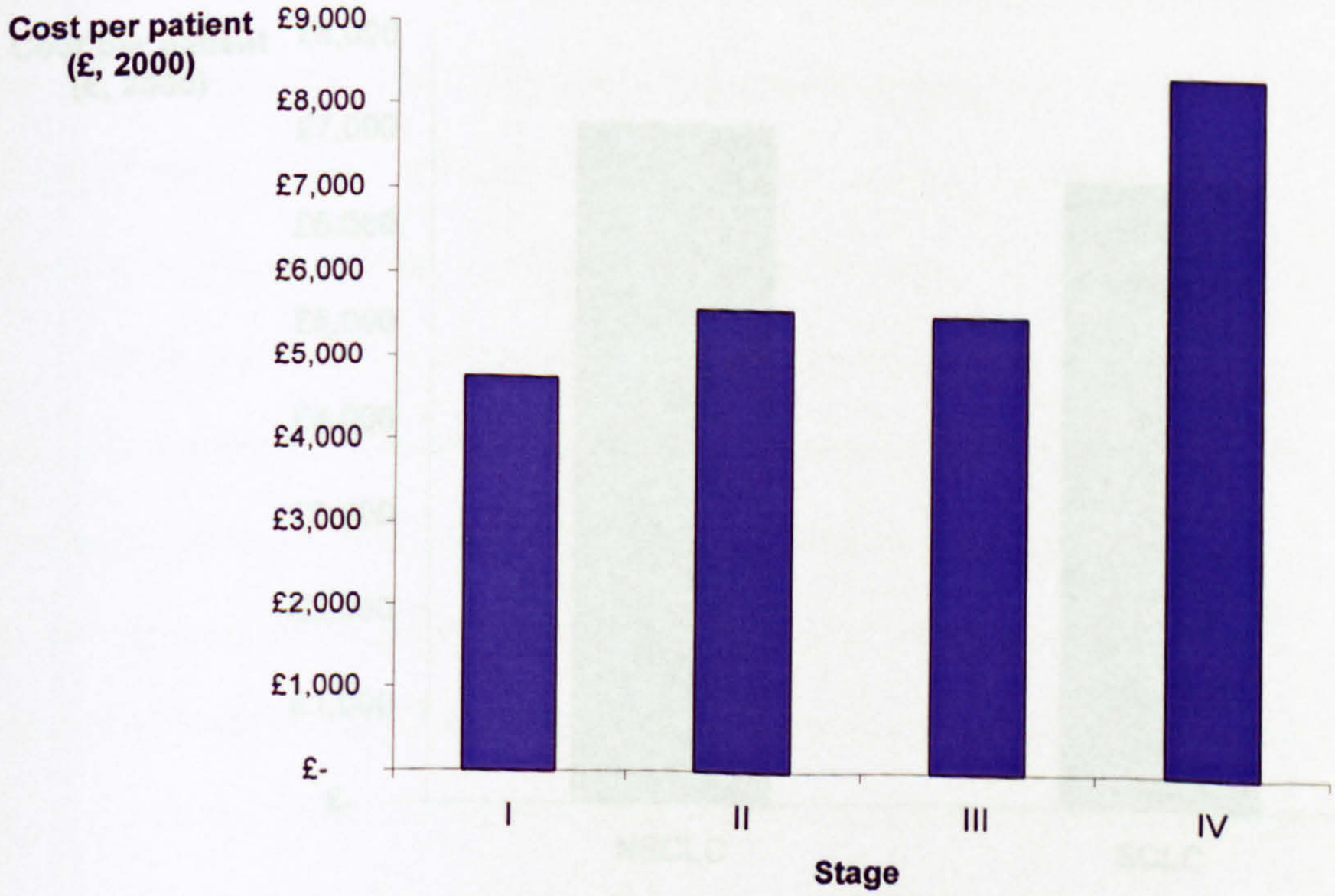


Figure 7.5 Cost by stage for colorectal cancer patients (UK £, 2000) (source:[35])

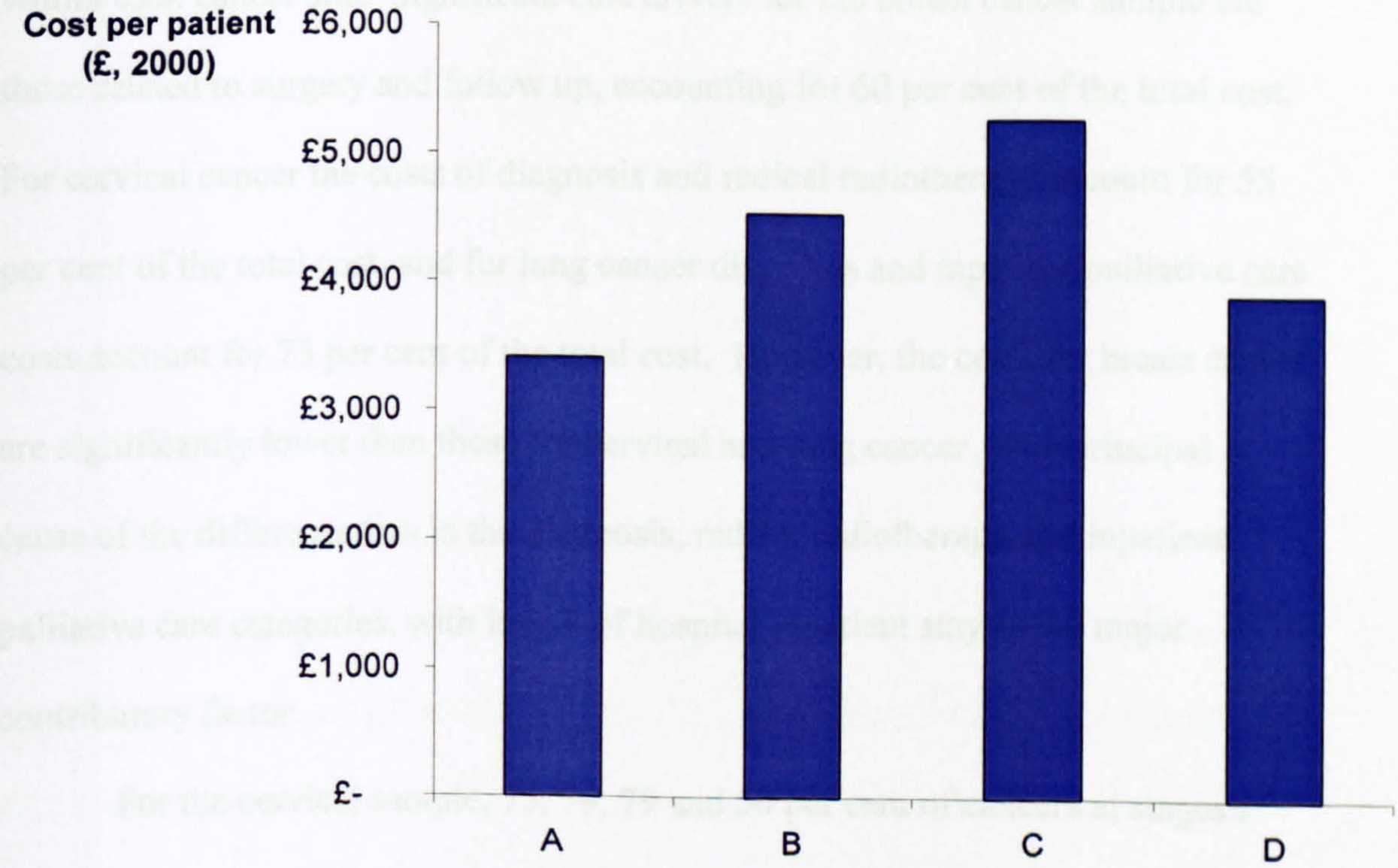


Figure 7.6 Cost by cell type for lung cancer patients (UK £, 2000)

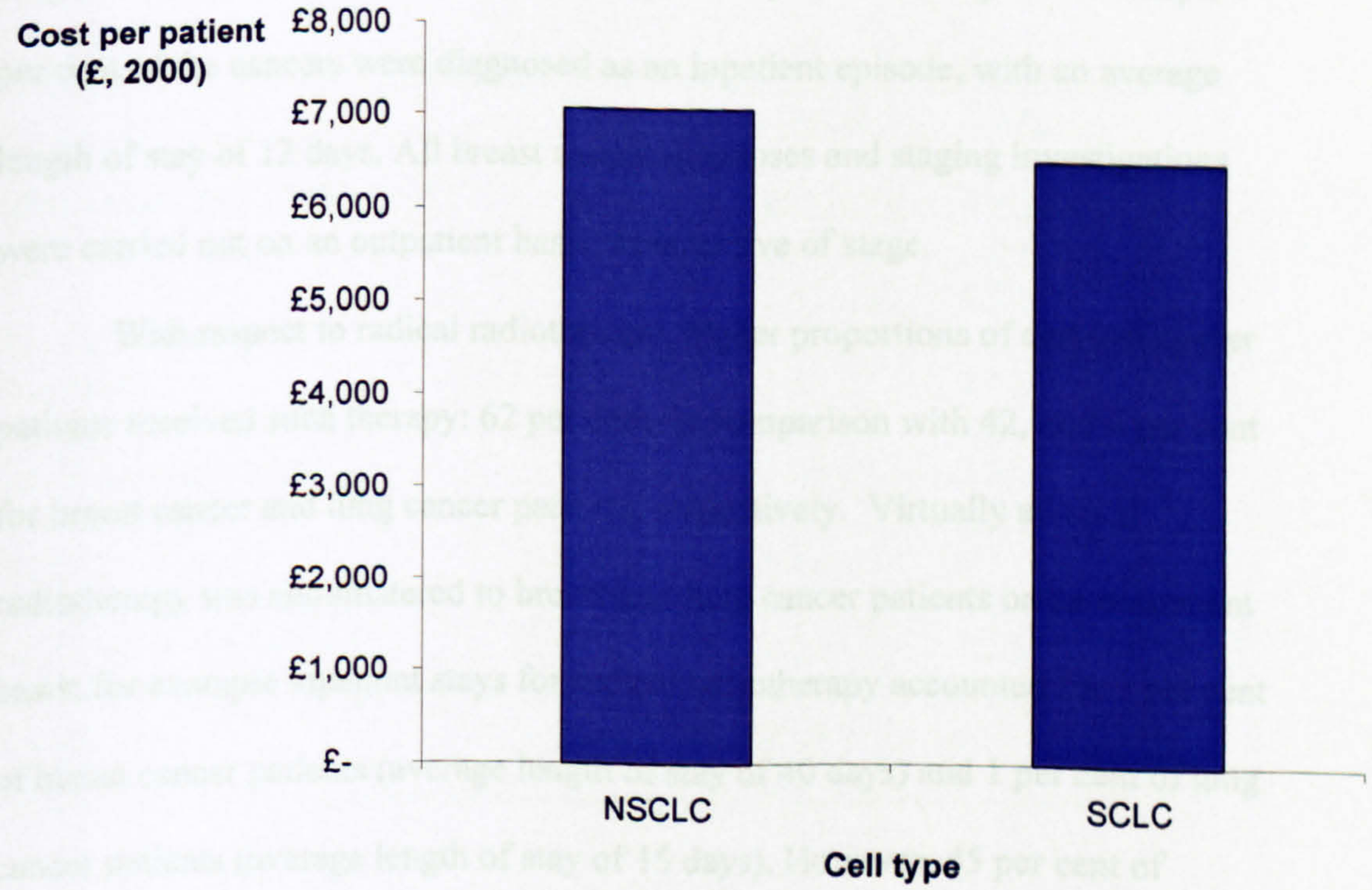


Table 7.10 displays the structure of the total cost estimates in more detail within each cancer site. Significant cost drivers for the breast cancer sample are those related to surgery and follow up, accounting for 60 per cent of the total cost. For cervical cancer the costs of diagnosis and radical radiotherapy account for 55 per cent of the total cost, and for lung cancer diagnosis and inpatient palliative care costs account for 73 per cent of the total cost. However, the costs for breast cancer are significantly lower than those for cervical and lung cancer. The principal cause of the difference lies in the diagnosis, radical radiotherapy and inpatient palliative care categories, with length of hospital inpatient stay as the major contributory factor.

For the cervical sample, 75, 79, 79 and 50 per cent of cancers at stages I through IV, respectively, were diagnosed on an inpatient basis, with average lengths of stay of 5, 9, 11 and 16 days, respectively. For the lung cancer sample 74 per cent of the cancers were diagnosed as an inpatient episode, with an average length of stay of 12 days. All breast cancer diagnoses and staging investigations were carried out on an outpatient basis, irrespective of stage.

With respect to radical radiotherapy, higher proportions of cervical cancer patients received such therapy: 62 per cent, in comparison with 42, and 4 per cent for breast cancer and lung cancer patients, respectively. Virtually all such radiotherapy was administered to breast and lung cancer patients on an outpatient basis: for example inpatient stays for radical radiotherapy accounted for 3 per cent of breast cancer patients (average length of stay of 40 days) and 1 per cent of lung cancer patients (average length of stay of 15 days). However, 45 per cent of

cervical cancer patients received radiotherapy as inpatients (average length of stay of 24 days).

Inpatient palliative care was employed by 45 per cent of the lung cancer patients, with an average length of stay of 22 days. This is compared with 20-22 per cent of breast and cervical cancer patients, with an average length of stay of 20 and 30 days respectively.

Although surgery represents the significant cost driver for breast cancer patients with 83 per cent of the breast cancer sample receiving surgery compared to 37 and 7 per cent of the cervical and lung cancer samples, the average length of stay was 5 days for breast cancer patients. Thus, the resultant surgery costs for breast cancer are more than offset by the higher costs associated with diagnosis, radical radiotherapy and inpatient palliative care for the cervical and lung cancer patients.

Table 7.10 Structure of total cost estimates within each cancer site

	Cervical	Breast	Lung
Mean total cost (£UK, 2000)	**£12315.13**	**£5035.50**	**£7016.01**
CI	11,051.72-13,578.52	4,442.38-5,618.62	6,007.22-8,024.80
% of total cost:			
Diagnosis	23.1	1.4	47.7
Surgery	9.3	39.6	6.0
Radical radiotherapy	32.6	13.6	2.8
Chemotherapy	2.1	2.7	1.8
Hormone therapy	0.3	1.2	-
Palliative radiotherapy	4.1	5.7	3.8
Inpatient palliative care	10.2	9.4	25.5
Investigations and complications	12.1	4.9	9.2
Follow up	6.1	21.3	3.3
Other	-	0.1	-

In conclusion, the comparison of the breast, cervical and lung cancer costs clearly indicates that the cost of cervical cancer is significantly higher than those incurred by lung and breast cancer patients, and in turn the hospital cost of lung cancer is significantly higher than that for breast cancer. The reason for the difference in cost appears to be as a direct result of a greater proportion of cervical and lung cancer patients undergoing longer inpatient lengths of stay compared with the breast cancer patients (see tables 5.6, 6.7 and 7.6 in chapters 5, 6 and 7). The second major finding of this empirical work highlights the implications for hospital costs by the progression of the disease through well defined stages, and how these costs differ between cancer sites. The hypothesis prior to the empirical work was that early stage disease by its nature would cost significantly less to diagnose and treat compared to late stage cancers. However, the work reported in chapters 5-7 show that by shifting the detection of the disease to the earliest invasive stage results in significant cost economies for cervical cancer, whereas the impact on overall cost for breast and colorectal cancer is minimal.

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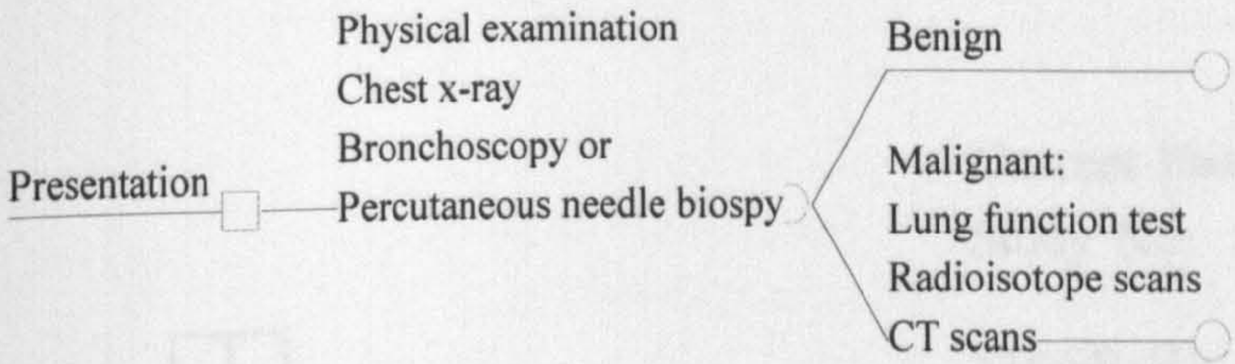
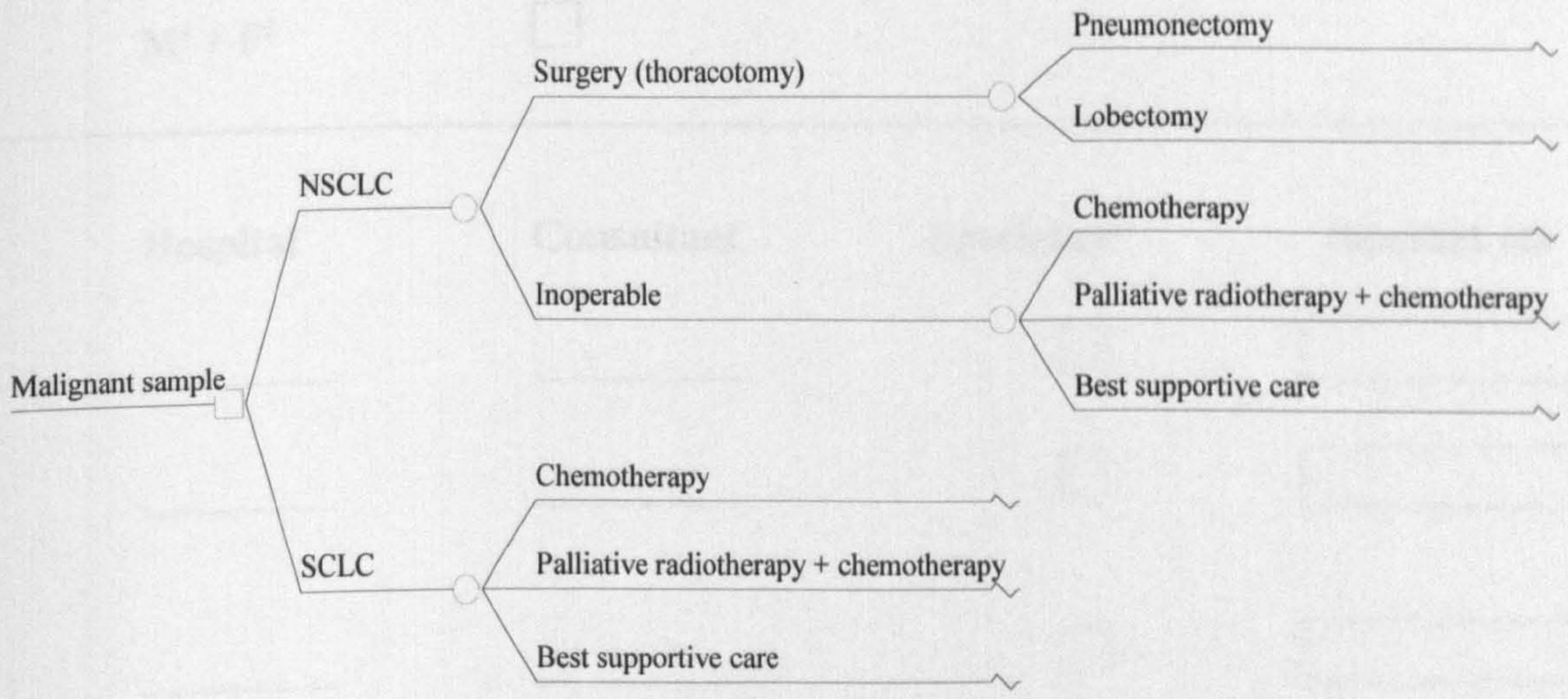
Appendix 7.1
Diagnosis/staging algorithm for cervical cancer from the literature



Treatment algorithm for breast cancer by stage from the literature.



Appendix 7.2 **CANCER IN TRENT** NON-SMALL CELL

LUNG CANCER ABSTRACT

DIAGNOSIS FORM

Abstracter: ☐☐☐

BASIC INFO

Current Date: ☐☐☐☐☐☐

Study No: ☐☐☐

District Code: ☐☐ TIHSR ID: ☐☐☐☐☐☐☐☐

Patient's Name: _____ Date of Birth: ☐☐☐☐☐☐

Clinical Trial: Yes[1] / No[2] ☐ Trial No: _____

Gender: M[1] / F[2] ☐

Treatment	Hospital	Consultant	Speciality*	Hospital No
Referral from:	_____	_____	☐	☐☐☐☐☐☐
Surgery:	_____	_____	☐	☐☐☐☐☐☐
Radiotherapy:	_____	_____	☐	☐☐☐☐☐☐
Chemotherapy:	_____	_____	☐	☐☐☐☐☐☐
Regular follow-up:	_____	_____	☐	☐☐☐☐☐☐

* Code as chest physician[1]/oncologist[2]/thoracic surgeon[3]/geriatrician[4]/consultant physician[5]/other consultant[6]/not recorded[9]

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

HISTORY

Duration of history of symptoms (weeks): _____ ☐☐☐

Mode of presentation: ☐
1 Symptoms
2 Routine chest X-ray
3 Other investigations for other disease
4 Other
9 Not recorded

If "other", please specify: _____

Smoking history: Smoker[1] / Non-smoker[2] / Ex-smoker[3] / Not recorded[9] ☐

Type: Cigarette[1] / Cigar[2] / Pipe[3] / Roll-up[4] / NA[8] / NR[9] ☐

If smoker: No smoked per day: ☐

$<10^{1}$ / 10-19[2] / 20-29[3] / 30+[4] / Light[5] / Medium[6] / Heavy[7] / NR[9]

No of years since started smoking: ☐

$<5^{1}$ / 5-9[2] / 10+[3] / Long term[4] / NR[9]

If ex-smoker: No of years since stopped smoking: ☐

$<1^{1}$ / 1-2[2] / 3-5[3] / 6-10[4] / $>10^{5}$ / NR[9]

Occupation of patient: _____

Performance Status: Grade 0[1]/Grade 1[2]/Grade 2[3]/Grade 3[4]/Grade 4[5]/Not recorded[9] ☐

Myocardial infarction: Yes($\leq$6mths)[1] / Yes($>$6mths)[2] / No[3] / Not recorded[9] ☐

History of angina: Yes[1] / No[2] / Not recorded[9] ☐

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

DIAGNOSIS

Investigations	1 Yes 2 No 9 Not recorded	Date of Investigation	1 IP 2 OP 3 DC	Date Admitted	Date Discharged
Chest X-ray Other X-ray: _____					
Sputum cytology					
Bronchoscopy: Fibre-optic Rigid					
Percutaneous needle biopsy					
FNA					
Lung biopsy					
Pleural biopsy					
Pleural aspiration					
Lymph-node biopsy					
Bone marrow aspiration					
Blood count					
Liver function test					
Lung function test					
Ultrasound					

continued .....

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

DIAGNOSIS (continued)

Investigations	1 Yes 2 No 9 Not recorded	Date of Investigation	1 IP 2 OP 3 DC	Date Admitted	Date Discharged
Isotope bone scan Other scan: _____					
CT scan: chest brain					
Mediastinoscopy/ mediastinotomy					
MRI scan: skeletal brain					
Thoracotomy: open closed					
Other: _____ _____					

Diagnosis continued overleaf

DIAGNOSIS (continued)

Date of diagnosis (d/m/y): ☐☐☐☐☐☐

Local spread (at diagnosis): Yes[1] / No[2] / Not recorded[9] ☐

Site of local spread: (at diagnosis) ☐
1 Mediastinum
2 Pleural space
3 Chest wall
4 Lymphatic spread
5 Other
9 Not recorded

If "other", please specify: _____

Contralateral spread: (at diagnosis) Yes[1] / No[2] / Not recorded[9] ☐

Metastasis (at diagnosis): Yes[1] / No[2] / Not recorded[9] ☐

Site of metastasis: (at diagnosis) ☐
1 Liver
2 Adrenal
3 Renal
4 Abdominal node
5 Brain
6 Bone
7 Other
9 Not recorded

If "other", please specify: _____

Study No: ☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

HISTOPATHOLOGY

Histology (attach copy of path report):

Date of report (d/m/y): ☐☐☐☐☐☐

Report no:

Type: ☐

1 Squamous cell
2 Small cell
3 Adenocarcinoma
4 Large cell
5 Adenosquamous ca
6 Carcinoid tumour
7 Mesothelioma
8 Other/Mixed type
9 Not recorded

If "Other/Mixed type", please specify: _____

Grade: Well[1] / moderately[2] / poorly differentiated[3] / not recorded[9] ☐

Pathological size (cm): _____ ☐☐.☐☐

Side of tumour: Left[1] / Right[2] / Bilateral[3] ☐

Location of tumour: ☐

1 Main bronchus
2 Upper lobe
3 Middle lobe
4 Lower lobe
5 Other
9 Not recorded

If "other", please specify: _____

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

STAGING OF NON-SMALL CELL LUNG CANCER

Pathological staging: pT ☐ pN ☐ pM ☐

Stage as given in notes: 0[1] / I[2] / II[3] / IIIa[4] / IIIb[5] / IV[6] / Not recorded[9] ☐

TREATMENT OF NON-SMALL CELL CANCER

Patient suitable for surgery Yes[1] / No[2] ☐

If "No",reason why patient not suitable: _____

Surgery: Yes[1] / No[2] ☐

Date admitted for surgery (d/m/y): ☐☐☐☐☐☐

Date of surgery (d/m/y): ☐☐☐☐☐☐

Date discharged following surgery (d/m/y): ☐☐☐☐☐☐

IP[1] / OP[2] / DC[3] ☐

Type of surgery: ☐

1 No removal (Thoracotomy)
2 Lobectomy
3 Segmentectomy
4 Pneumonectomy
5 Other
9 Not specified

If "other", please specify: _____

Length of operation (hrs/mins): ☐☐hrs☐☐mins

TREATMENT OF NON-SMALL CELL CANCER (continued)

Radiotherapy:
Yes[1] / No[2] ☐
Radical[1] / Palliative[2] ☐

Dose:
Radiation dose (total dose cGy) _____
No of fractions _____

Duration of RT:
Date started: ☐☐☐☐☐☐
Date finished: ☐☐☐☐☐☐

IP[1] / OP[2] / DC[3] ☐

Site:
Chest[1] / Bone[2] / Brain[3] / Other[4] ☐

If "other", please specify: _____

Further Radiotherapy:
Yes[1] / No[2] ☐
Radical[1] / Palliative[2] ☐

Dose:
Radiation dose (total dose cGY) _____
No of fractions _____

Duration of RT:
Date started: ☐☐☐☐☐☐
Date finished: ☐☐☐☐☐☐

IP[1] / OP[2] / DC[3] ☐

Site:
Chest[1] / Bone[2] / Brain[3] / Other[4] ☐

If "other", please specify: _____

TREATMENT OF NON-SMALL CELL CANCER (continued)

Chemotherapy: Yes[1] / No[2] ☐

Single agent[1] / Combination[2] ☐

Active Drugs	Course/ Cycle	Drug Code	Dose	Date Started	Date Finished	1 IP 2 OP 3 DC

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

FOLLOW UP/OUTCOME

	Frequency of Investigations per Year				
Investigation	**1993**	**1994**	**1995**	**1996**	**1997**
OP check up					
Chest X-ray					
Other X-ray					
CT scan					
Bone scan					
Ultrasound					
Blood count					
Transfusion					
Lung function test					
Biochemistry					
Haematology					
Microbiology					
Other _____ _____					

Local recurrence, distant metastases, vital status

Local recurrence: Yes[1] / No[2] / Not applicable[8] / Not recorded[9] ☐

Date of first local recurrence(d/m/y): ☐☐☐☐☐☐

Site of local recurrence: ☐

1 Mediastinum
2 Pleural space
3 Chest wall
4 Lymphatic spread
5 Other
9 Not recorded

If "other", please specify: _____

Contralateral lung recurrence: Yes[1] / No[2] / Not applicable[8] / Not recorded[9] ☐

Date of first contralateral lung recurrence (d/m/y): ☐☐☐☐☐☐

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

FOLLOW UP/OUTCOME (continued)

Development of distant metastasis: Yes[1] / No[2] / Not applicable[8] / Not recorded[9] ☐
(after diagnosis)

Date of first distant metastasis (d/m/y): ☐☐☐☐☐☐
(after first diagnosis)

Site of first distant metastasis: ☐
(after first diagnosis)

1 Liver
2 Adrenal
3 Renal
4 Abdominal node
5 Brain
6 Bone
7 Other
9 Not recorded

If "other", please specify: _____

Palliative care: Yes(IP)[1] / No[2] / Yes(GP)[3] / Not applicable[8] / Not recorded[9] ☐

If Inpatient:

Date admitted (d/m/y): ☐☐☐☐☐☐

Date discharged (d/m/y): ☐☐☐☐☐☐

Outcome:

Vital status: Dead[1] / Alive[2] ☐

Date of death/date last seen: ☐☐☐☐☐☐

COMMENTS:

CANCER IN TRENT

SMALL CELL

LUNG CANCER ABSTRACT

DIAGNOSIS FORM

Abstracter: ☐☐☐

BASIC INFO

Current Date: ☐☐☐☐☐☐

Study No: ☐☐☐

District Code: ☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐☐

Patient's Name: _____

Date of Birth: ☐☐☐☐☐☐

Clinical Trial: Yes[1] / No[2] ☐

Trial No: _____

Gender: M[1] / F[2] ☐

Treatment	Hospital	Consultant	Speciality*	Hospital No
Referral from:	_____	_____	☐	
Surgery:	_____	_____	☐	
Radiotherapy:	_____	_____	☐	
Chemotherapy:	_____	_____	☐	
Regular follow-up:	_____	_____	☐	

* Code as chest physician[1]/oncologist[2]/thoracic surgeon[3]/geriatrician[4]/consultant physician[5]/other consultant[6]/not recorded[9]

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

HISTORY

Duration of history of symptoms (weeks): _____ ☐☐☐

Mode of presentation: ☐
1 Symptoms
2 Routine chest X-ray
3 Other investigations for other disease
4 Other
9 Not recorded

If "other", please specify: _____

Smoking history: Smoker[1] / Non-smoker[2] / Ex-smoker[3] / Not recorded[9] ☐

Type: Cigarette[1] / Cigar[2] / Pipe[3] / Roll-up[4] / NA[8] / NR[9] ☐

If smoker: No smoked per day: ☐

$<10^{1}$ / 10-19[2] / 20-29[3] / 30+[4] / Light[5] / Medium[6] / Heavy[7] / NR[9]

No of years since started smoking: ☐

$<5^{1}$ / 5-9[2] / 10+[3] / Long term[4] / NR[9]

If ex-smoker: No of years since stopped smoking: ☐

$<1^{1}$ / 1-2[2] / 3-5[3] / 6-10[4] / $>10^{5}$ / NR[9]

Occupation of patient: _____

Performance Status: Grade 0[1]/Grade 1[2]/Grade 2[3]/Grade 3[4]/Grade 4[5]/Not recorded[9] ☐

Myocardial infarction: Yes($\leq$6mths)[1] / Yes($>$6mths)[2] / No[3] / Not recorded[9] ☐

History of angina: Yes[1] / No[2] / Not recorded[9] ☐

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

DIAGNOSIS

Investigations	1 Yes 2 No 9 Not recorded	Date of Investigation	1 IP 2 OP 3 DC	Date Admitted	Date Discharged
Chest X-ray Other X-ray: _____					
Sputum cytology					
Bronchoscopy: Fibre-optic Rigid					
Percutaneous needle biopsy					
FNA					
Lung biopsy					
Pleural biopsy					
Pleural aspiration					
Lymph node biopsy					
Bone marrow aspiration					
Blood count					
Liver function test					
Lung function test					
Ultrasound					

continued .....

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐

DIAGNOSIS (continued)

Investigations	1 Yes 2 No 9 Not recorded	Date of Investigation	1 IP 2 OP 3 DC	Date Admitted	Date Discharged
Isotope bone scan Other scan: _____					
CT scan: chest brain					
Mediastinoscopy/ mediastinotomy					
MRI scan: skeletal brain					
Thoracotomy: open closed					
Other: _____ _____					

Diagnosis continued overleaf

DIAGNOSIS (continued)

Date of diagnosis (d/m/y): ☐☐☐☐☐☐

Local spread (at diagnosis): Yes[1] / No[2] / Not recorded[9] ☐

Site of local spread:
(at diagnosis)

1 Mediastinum
2 Pleural space
3 Chest wall
4 Lymphatic spread
5 Other
9 Not recorded

☐

If "other", please specify: _____

Contralateral spread:
(at diagnosis)

Yes[1] / No[2] / Not recorded[9] ☐

Metastasis (at diagnosis): Yes[1] / No[2] /Not recorded[9] ☐

Site of metastasis:
(at diagnosis)

1 Liver
2 Adrenal
3 Renal
4 Abdominal node
5 Brain
6 Bone
7 Other
9 Not recorded

☐

If "other", please specify: _____

HISTOPATHOLOGY

Histology (attach copy of path report):

Date of report (d/m/y): ☐☐☐☐☐☐

Report no:

Type: ☐

1 Squamous cell
2 Small cell
3 Adenocarcinoma
4 Large cell
5 Adenosquamous ca
6 Carcinoid tumour
7 Mesothelioma
8 Other/Mixed type
9 Not recorded

If "Other/Mixed type", please specify: _____

Grade: Well[1] / moderately[2] / poorly differentiated[3] / not recorded[9] ☐

Pathological size (cm): _____ ☐☐.☐☐

Side of tumour: Left[1] / Right[2] / Bilateral[3] ☐

Location of tumour: ☐

1 Main bronchus
2 Upper lobe
3 Middle lobe
4 Lower lobe
5 Other
9 Not recorded

If "other", please specify: _____

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

STAGING OF SMALL CELL LUNG CANCER

Specified in notes: Yes[1] / No[2] ☐

Extent of disease:
1 Limited (confined to one side of thorax with or without enlarged supraclavicular nodes) ☐
2 Extensive (all other patients)

TREATMENT OF SMALL-CELL LUNG CANCER

Chemotherapy: Yes[1] / No[2] ☐

Single agent[1] / combination[2] ☐

Active Drugs	Course/ Cycle	Drug Code	Dose	Date Started	Date Finished	1 IP 2 OP 3 DC

TREATMENT OF SMALL CELL LUNG CANCER (continued)

Radiotherapy:	Yes[1] / No[2]	☐
	Radical[1] / Palliative[2]	☐
Dose:	Radiation dose (total dose cGy)	_____
	No of fractions	_____
Duration of RT:	Date started:	☐☐☐☐☐☐
	Date finished:	☐☐☐☐☐☐
	IP[1] / OP[2] / DC[3]	☐
Site:	Chest[1] / Bone[2] / Brain[3] / Other[4]	☐
If "other",please specify:	_____	
Further Radiotherapy:	Yes[1] / No[2]	☐
	Radical[1] / Palliative[2]	☐
Dose:	Radiation dose (total dose cGy)	_____
	No of fractions	_____
Duration of RT:	Date started:	☐☐☐☐☐☐
	Date finished:	☐☐☐☐☐☐
	IP[1] / OP[2] / DC[3]	☐
Site:	Chest[1] / Bone[2] / Brain[3] / Other[4]	☐
If "other",please specify:	_____	

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

TREATMENT OF SMALL CELL LUNG CANCER (continued)

Surgery: Yes[1] / No[2] ☐

Date admitted for surgery: ☐☐☐☐☐☐

Date of surgery: ☐☐☐☐☐☐

Date discharged following surgery: ☐☐☐☐☐☐

IP[1] / OP[2] / DC[3] ☐

Type of surgery: ☐

1 No removal (Thoracotomy)
2 Lobectomy
3 Segmentectomy
4 Pneumonectomy
5 Other
9 Not specified

If "other", please specify: _____

Length of operation (hrs/mins): ☐☐hrs☐☐mins

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

FOLLOW UP/OUTCOME

	Frequency of Investigations per Year				
Investigation	**1993**	**1994**	**1995**	**1996**	**1997**
OP check up					
Chest X-ray					
Other X-ray					
CT scan					
Bone scan					
Ultrasound					
Blood count					
Transfusion					
Lung function test					
Biochemistry					
Haematology					
Microbiology					
Other _____ _____					

Local recurrence, distant metastases, vital status

Local recurrence: Yes[1] / No[2] / Not applicable[8] / Not recorded[9] ☐

Date of first local recurrence(d/m/y): ☐☐☐☐☐☐

Site of local recurrence: ☐

1 Mediastinum
2 Pleural space
3 Chest wall
4 Lymphatic spread
5 Other
9 Not recorded

If "other", please specify: _____

Contralateral lung recurrence: Yes[1] / No[2] / Not applicable[8] / Not recorded[9] ☐

Date of first contralateral lung recurrence (d/m/y): ☐☐☐☐☐☐

Study No: ☐☐☐

TIHSR ID: ☐☐☐☐☐☐☐☐

FOLLOW UP/OUTCOME (continued)

Development of distant metastasis: Yes[1] / No[2] / Not applicable[8] / Not recorded[9] ☐
(after diagnosis)

Date of first distant metastasis (d/m/y): ☐☐☐☐☐☐
(after first diagnosis)

Site of first distant metastasis: ☐
(after first diagnosis)

1 Liver
2 Adrenal
3 Renal
4 Abdominal node
5 Brain
6 Bone
7 Other
9 Not recorded

If "other", please specify: _____

Palliative care: Yes(IP)[1] / No[2] / Yes(GP)[3] / Not applicable[8] / Not recorded[9] ☐

If Inpatient:

Date admitted (d/m/y): ☐☐☐☐☐☐

Date discharged (d/m/y): ☐☐☐☐☐☐

Outcome:

Vital status: Dead[1] / Alive[2] ☐

Date of death/date last seen: ☐☐☐☐☐☐

COMMENTS:

Appendix 7.3: Resource-use by cell type years 1-4 - Lung Cancer

YEAR 1	NSCLC	SCLC
Diagnosis		
chest X-ray	215 (94%)	26 (100%)
other X-ray	27 (12%)	2 (8%)
sputum cytology	67 (29%)	9 (35%)
bronchoscopy	128 (56%)	18 (69%)
percutaneous needle biopsy	15 (7%)	1 (4%)
FNA	13 (6%)	-
lung biopsy	94 (41%)	-
pleural biopsy	8 (4%)	1 (4%)
lymph node biopsy	8 (4%)	4 (16%)
pleural aspiration	19 (8%)	3 (12%)
bone marrow aspiration	2 (1%)	1 (4%)
blood count	205 (90%)	23 (89%)
liver function test	143 (63%)	16 (62%)
lung function test	112 (49%)	7 (27%)
ultrasound	43 (19%)	9 (5%)
bone scan	21 (9%)	3 (12%)
mediastinoscopy	4 (2%)	-
CT scan	97 (42%)	12 (47%)
MRI scan	3 (1%)	1 (4%)
Treatment		
Surgery	17 (8%)	-
thoracotomy	3 (1%)	-
lobectomy	8 (4%)	-
segmentectomy	1 (1%)	-
pneumonectomy	4 (2%)	-
Radical radiotherapy	9 (4%)	2 (8%)
Secondary RRT	6 (3%)	-
Third RRT	1 (1%)	-
Chemotherapy	4 (2%)	15 (58%)
secondary chemotherapy	-	1 (4%)
Inpatient investigation	37 (16%)	6 (23%)
second investigation	10 (4%)	3 (12%)
third investigation	2 (1%)	2 (8%)
Palliative radiotherapy	79 (35%)	13 (50%)
secondary PRT	9 (4%)	1 (4%)
third PRT	2 (1%)	-
fourth PRT	1 (1%)	-
Inpatient palliative care	92 (41%)	10 (38%)

Follow up (year 1)	NSCLC	SCLC
outpatient visit	88 (39%)	13 (50%)
chest x-ray	82 (36%)	15 (57%)
other x-ray	13 (6%)	7 (27%)
CT scan	24 (11%)	2 (8%)
bone scan	18 (9%	3 (12%)
ultrasound	9 (4%)	3 (12%)
lung function test	10 (4%)	3 (12%)
ECG	35 (15%)	6 (23%)
bronchoscopy	4 (2%)	-
sputum cytology	1 (1%)	-
biochemistry	70 (31%)	12 (46%)
blood count	77 (34%)	14 (54%)
microbiology	17 (7%)	4 (15%)
YEAR 2		
Treatment		
Inpatient investigation	4 (2%)	-
second investigation	4 (2%)	-
third investigation	-	1 (4%)
second chemotherapy	-	1 (4%)
secondary PRT	2 (1%)	1 (15%)
Inpatient palliative care	7 (3%)	1 (15%)
Follow up		
outpatient visit	25 (11%)	4 (4%)
chest x-ray	16 (7%)	4 (4%)
other x-ray	2 (1%)	-
CT scan	5 (2%)	1 (4%)
bone scan	2 (1%)	1 (4%)
ultrasound	3 (1%)	1 (4%)
lung function test	2 (1%)	1 (4%)
ECG	4 (2%)	-
bronchoscopy	2 (1%)	-
sputum cytology	1 (1%)	-
biochemistry	9 (4%)	1 (4%)
blood count	8 (4%)	1 (4%)
microbiology	4 (2%)	-

YEAR 3	NSCLC	SCLC
Treatment		
Inpatient investigation	3 (1%)	-
second investigation	1 (1%)	-
Palliative radiotherapy	3 (1%)	-
secondary PRT	1 (1%)	-
Inpatient palliative care	3 (1%)	-
Follow up		
outpatient visit	14 (6%)	-
chest x-ray	8 (4%)	1 (4%)
other x-ray	1 (1%)	-
CT scan	2 (1%)	-
bone scan	1 (1%)	-
ultrasound	4 (2%)	-
lung function test	2 (1%)	-
ECG	4 (2%)	-
bronchoscopy	-	-
sputum cytology	1 (1%)	-
biochemistry	5 (2%)	-
blood count	7 (3%)	-
microbiology	6 (3%)	-
YEAR 4		
Treatment		
secondary investigation	1 (1%)	-
third investigation	1 (1%)	-
fourth investigation	1 (1%)	-
Inpatient palliative care	2 (1%)	-
Follow up		
outpatient visit	9 (4%)	-
chest x-ray	7 (3%)	1 (4%)
other x-ray	-	-
CT scan	3 (1%)	-
bone scan	-	-
ultrasound	-	-
lung function test	-	-
ECG	-	-
bronchoscopy	3 (1%)	-
sputum cytology	-	-
biochemistry	3 (1%)	-
blood count	-	-
microbiology	-	-

Chapter 8

Appropriate statistical analysis of cost data

8.1 Introduction

In the previous three chapters (5,6 and 7) all the analysis of the cost data was undertaken using parametric tests such as the t-test and analysis of variance. Parametric tests require the assumption of normality, however, due to its skewed nature, resource use and cost data pose problems for using these types of tests. Given the problems with the distributional nature of the data there has been a recent increase in the interest of how cost data for use in economic evaluations should be appropriately analysed(1-8). There are a number of proposed methods to overcome this problem including; removal of the outliers causing the data to be non-normal, transformation of data, use of 'distribution free' methods such as non-parametric statistics and bootstrapping. The original data used in the previous three costing chapters are skewed, therefore the aim of this chapter is to firstly explore each of the proposed methods for analysing skewed data, and secondly to ascertain whether use of parametric tests led to the wrong conclusions being drawn in chapters 5-7.

8.2 Skewed cost data

The value of skew for a particular data set measures the asymmetry of its distribution. The expected value of skew for a symmetric distribution (i.e. the normal distribution) is zero. A distribution with a significant positive skew has a long right tail. A

distribution with a significant negative skewness has a long left tail. A skew value greater than 1 generally indicates a distribution that differs significantly from a normal distribution.

Health care resource use and costs are typically positively skewed because(2, 5, 9):

- It is impossible to have negative costs or counts of resource used
- Invariably a few patients incur very high costs, for example due to long inpatient length of stays.

In order to explore the distribution of the data, summary statistics such as the measure of central tendency i.e. the mean or median, the measure of dispersion i.e. standard deviation or quartiles and skew can be backed up by a graphic representation of the data in the form of a histogram. If the data are positively skewed it is certain that the mean value will be much higher than the median value. Other rules of thumb are that if the standard deviation is twice the value of the mean the data is likely to be skewed(10). Formal tests for skew exist (these are actually tests for normality of the data), the Shapiro-Wilk and Kolmogorov-Smirnov tests. With the Shapiro-Wilk test the test statistic gives a value from 0 to 1 with 1 indicating normality. The Kolmogorov-Smirnov test is used to test the hypothesis that a sample comes from a particular distribution (i.e. normal). The value of the Kolmogorov-Smirnov Z is based on the largest absolute difference between the observed and the theoretical cumulative distributions.

8.3 Methods for the appropriate analysis with skewed cost data

An estimate of the average or arithmetic mean cost is paramount to any costing exercise. Decision-makers and planners in any health care system require knowledge of the total budget over a specified period of time (usually financial/budgetary year) that is necessary in order to provide a particular intervention or treatment to a group of patients. The average cost estimate multiplied by the patient numbers requiring the treatment or intervention produces such an estimate of total cost. Invariably, as health economists we require some formal comparison of the average per patient costs of one particular group of patients with the average per patient costs for another distinct group of patients, this cost difference is used as the numeraire for calculating cost-effectiveness ratios. However, there is concern over using standard parametric statistical techniques such as the t-test, analysis of variance and ordinary-least squares regression where the data used for the analysis are skewed (as in the case for cost data). The above techniques rely on the assumption of normality of the data. And although, these standard methods for analysing arithmetic means are known to be fairly robust to non-normality, the robustness depends on the sample size and the severity of the skew of the data, and no criteria exist for judging whether the analysis will be robust enough for a particular dataset. Therefore various standard textbook methods have been proposed as ways of analysing skewed data(11).

8.3.1 Median

In the presence of skewed data it is often common to report the median rather than the mean, however, although the median is useful to present alongside the mean, it is inappropriate to use in any cost or cost-effectiveness analysis. The reason is that we

are interested in the average per patient cost which provides information on the total cost of care to a particular patient group when combined with the total number of patients requiring that specified care. With positively skewed data the median value will be lower than the mean value, and using the product of the median value and the number of patients requiring the intervention will not give the total cost of the intervention for that group.

8.3.2 Exclusion of outliers

The exclusion of outliers is a method that is often used by statisticians and has been suggested for use with cost data(2). Once outliers are removed, a smoother distribution of costs is likely to be obtained, allowing statistical analysis of the differences in mean costs between specified groups using parametric statistical tests. However, one can argue that by excluding the outliers in a positively skewed dataset you are disposing of important information that will enable policy makers to determine the total budget involved with implementing one treatment compared to another. The excluded data in a cost dataset are likely to be for those patients incurring particularly high or low costs, hence using estimates from a restricted dataset will result in an under-estimate of the likely total budget required. However, in situations where a few patients have very low or high costs it may still be appropriate.

8.3.3 Transformation

Another method used by statisticians when controlling for skewed data is to transform the data onto another scale. Transformation can have the effect of normalising the data and equalising the variance when comparing two datasets. Usual methods of transforming the data include taking the natural logarithm, reciprocal or square root.

The data are then analysed using parametric statistical tests such as the student t-test etc. However transformation can lead to problems of interpretation for the analysis of cost data. First, analyses using such transformed data are not addressing inferences about the arithmetic mean cost. It is not clear what the reported difference actually means on a transformed scale, the original scale (i.e., currency units), is required to enable proper interpretation. Therefore, second it is necessary to 'back-transform' the point estimate of the difference in the mean value and the measure of variation or measure of precision of this mean value by taking the inverse function. This can only be done for transformations using the natural logarithm, by taking the exponential of the natural log value of the mean estimate. However, interpretation of this back-transformed value is still problematic, the value actually produced is the geometric mean and suffers the same problems as using the median. Back-transformation of the square root or reciprocal is completely meaningless. There is a nonparametric method proposed by Duan in 1983 to adjust the back-transformed data for any bias incurred after fitting a linear regression model on a transformed scale, this is known as the 'smearing estimator'(14). Cost analysis using data on a transformed scale have been undertaken in a number of studies. A UK based study, report their cost data for patients with mental health problems to be highly variable and positively skewed(12). They transformed all their cost data to natural logarithms before undertaking further analyses. Adams Dudley and colleagues also transformed their cost data by taking the natural logarithm, which reduced the skew, but was not sufficient to produce a normal distribution of the costs or the residuals when undertaking an OLS regression of their cost data(13). Rutten van Molken and colleagues undertook a multivariate regression

analysis of longitudinal skewed cost data(1). They suggest a four-step procedure for the analysis of skewed data (1994:339-342):

1. Transformation - a simple logarithmic transformation
2. Regression analysis - ordinary least squares regression
3. Calculation of the standardized expected costs
4. Retransformation - requires the expected costs on the untransformed scale.

The authors argue that to obtain the expected costs on an untransformed scale (e.g. UK £ sterling) it is inappropriate to simply take the exponential function of the estimated mean of the transformed costs as the retransformed costs will be neither unbiased nor consistent, unless the transformation was linear. They therefore suggest using a non-parametric retransformation factor called a 'smearing estimator'(14).

The corresponding equations for the four-step procedure are outlined below, where Y_i is the observed variable on the untransformed scale, X_i is the vector of explanatory variables, β is a column vector of unknown parameters to be estimated and ε_i is the residual error.

1. $Z_i = \mathrm{Ln}(Y_i)$
2. $Z_i = \alpha + X_i\beta + \varepsilon_i$
3. $\hat{Z}_i = \hat{\alpha} + X_i\hat{\beta}$
4. $E(Y_i/X_i) = \phi \cdot \exp(\alpha + X_i\beta)$

Where ϕ is a retransformation factor that can be estimated by:

$$\hat{\phi} = (\sum \exp(\hat{\varepsilon}_i)/ N$$

where $\hat{\varepsilon}$ is defined as $Z_i - \hat{\alpha} - X_i\hat{\beta}$ (a smearing estimator)

8.3.4 Nonparametric tests

Nonparametric statistics allow hypothesis testing even when certain classical assumptions such as normality of the data are violated. There are a number of tests that can be employed for the purpose of comparison of two or more independent groups; the Mann-Whitney test (for two independent samples) and the Kruskal-Wallis test (for three or more independent samples). The assumption underlying these tests is that the shape and variance of the distribution of the independent samples are the same, and the test relates to the difference in location of the two distributions. Unfortunately, this method runs into the problem of not providing information about the mean cost.

8.3.5 Bootstrapping

There is a nonparametric technique that allows for a comparison in the mean cost between two or more patient groups(5, 9, 15). Bootstrapping involves an extensive resampling procedure of an original sample to empirically provide an estimate of the statistics' sampling distribution. Given an original sample one takes a random re-sample with replacement[8.1] to yield a bootstrap sample of size n_i and then the statistic of interest can be calculated. This process is repeated many times (1000 times by convention) to yield a vector of bootstrap estimates of the statistic of interest (in the case of costs; mean cost). Due to replacement the bootstrap sample of cost data may include the costs for some patients more than once while excluding the costs for other patients completely. The sampling with replacement allows for variation between the samples. The standard deviation of the bootstrap means is equivalent to the standard

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8.1 'Replacement' means that once a random value has been used for the bootstrap resample it is put back into the original sample.

error of the mean estimate using parametric statistics. Several approaches exist to estimate confidence intervals using the bootstrap estimate of the sampling distribution(15, 16). However, the simplest method is the percentile method. The upper and lower CI are obtained using the $(\alpha/2)100$ and $(1-\alpha/2)100$ percentiles of the empirical sampling distribution. If using 1000 bootstrap re-samples the values for the 95% confidence limits correspond to the 26th and 975th points in the rank ordered vector of bootstrap means. These points are chosen since this excludes 25 values, (25/1000 = 2.5%) at either end of the estimated distribution.

The validity of the method rests on two assumptions. First, as the original sample size approaches the population size, the sample distribution will tend towards the population distribution, second, as the number of bootstrap replications increases the bootstrap estimate of the sampling distribution of the chosen statistic approaches the true sampling distribution.

8.4 Empirical investigation of methods used for analysing cost data

Recently there have been a number of commentaries on the appropriate methods for analysing cost data with no definite conclusions about the relative merits of each of these methods(1-8). Suggestions have included use of parametric tests on data with the outliers removed, or on transformed data, non-parametric tests, or more recently the non-parametric bootstrap method. Zhou (1997), and Thompson and Barber (2000) have independently of one another shown how results may change according to the method of analysis used, however the direction of the change cannot be predicted.

Thompson and Barber have concluded that in their experience, the results from the standard t-test are adequate for most comparative cost situations (8:1199).

With the aid of the data collected for the purpose of estimating the costs of breast, cervical and lung cancer I have investigated the use of the methods outlined above (section 8.2) for the univariate analysis of skewed cost data. Each cancer site has been explored in turn, with descriptions of and histograms displaying the data in terms of mean, median, standard deviation, 95 % confidence intervals and skew. The methods used include, parametric tests ignoring the issue of skewed data and then after the removal of outliers (removal of the five highest and five lowest values indicated by SPSS), and after transformation of the data (using three methods; the natural logarithm, the square root and the reciprocal), nonparametric tests and bootstrapping the data.

8.4.1 Breast cancer

The cost data and descriptive statistics for breast cancer by stage of disease are displayed in figures 8.1-8.6 for each of the methods explored. It is interesting to note that the distribution of the original cost data does not significantly differ from normality for stage IV cancers, whereas the distribution for stages I-III data do display a significant positive skew. The absolute value of the Shapiro-Wilk ranges from 0.56, 0.87, 0.85 and 0.87 (P = 0.03, 0.05, 0.01, 0.28) for stages I to IV respectively (where the absolute value ranges from 0-1, with 1 indicating normality) and similar results from the Kolmogorov Smirnov test (P =0.000, 0.037, 0.019, 0.164, indicating that the cost distributions for stages I-III differ significantly from normality). Lack of stage IV patients meant that outliers could only be removed for stages I-III, however, the

original cost data for stage IV cancers did not appear to be skewed. This has the effect of reducing the skew (Kolmogorov Smirnov test P =0.017, 0.070, 0.200, 0.164). Transforming the data using the natural logarithm and square root has the effect of reducing the skew, in fact changing from positive skew to negative skew using the Ln(cost), transforming the data also has the effect of equalising the variances between the stages. Transformation using the reciprocal worsens the skew for all four stages. Finally, figure 8.6 displays the histogram for the bootstrap estimate of the sampling distribution of the breast cost data. The bootstrap sampling distributions for each stage indicate that the sample size is sufficiently large that the assumption of normality for the use of parametric hypothesis testing is justified.

In the previous chapters I was interested in the comparison of costs between stages of disease. Here I have chosen to explore the difference in costs between early stage and late stage disease. All cancers diagnosed at stage I represent early stage disease, whereas cancers diagnosed at stages II–IV represent late stage disease(17). Table 8.1 displays the results using the parametric t-test on the original cost data, after removal of outliers and after transforming the data, and the nonparametric Mann-Whitney test to explore the difference between early and late stage cancer costs. Only when the outliers are removed is there a reported significant cost difference between early and late stage cancers. The nonparametric Mann-Whitney results in no significant difference between early and late stage costs (P = 0.139). Finally, the bootstrap estimate of the sampling distribution of the mean cost difference was found to be £950 (equivalent to the median), with a standard deviation around this mean of 600 (this standard deviation is equivalent to the standard error of the mean difference

using parametric statistics), and 95 % confidence intervals ranging from £-240-£2,142 (see Figure 8.7).

Table 8.1 Results of parametric and nonparametric analysis of difference in early stage and late stage costs – Breast cancer

Data	Stage	N	Mean	SD	Mean difference	Test statistic	P value	Skew
Original	Early	102	3,734	2,469	1,011	1.89	0.06	1.75
	Late	35	4,745	3,412				1.20
Outliers	Early	93	3,480	1,697	1,002	2.35	0.02	0.99
removed	Late	29	4,482	2,786				1.17
Ln	Early	102	7.99	0.78	2.06	1.35	0.18	-1.54
transformed	Late	35	8.20	0.79				-0.63
Square root	Early	102	0.0006	0.001	-1.59	-0.84	0.40	0.45
transformed	Late	35	0.0004	0.0005				0.49
Mann Whitney							0.14	

Figure 8.1 Histogram of original breast cancer cost data by stage

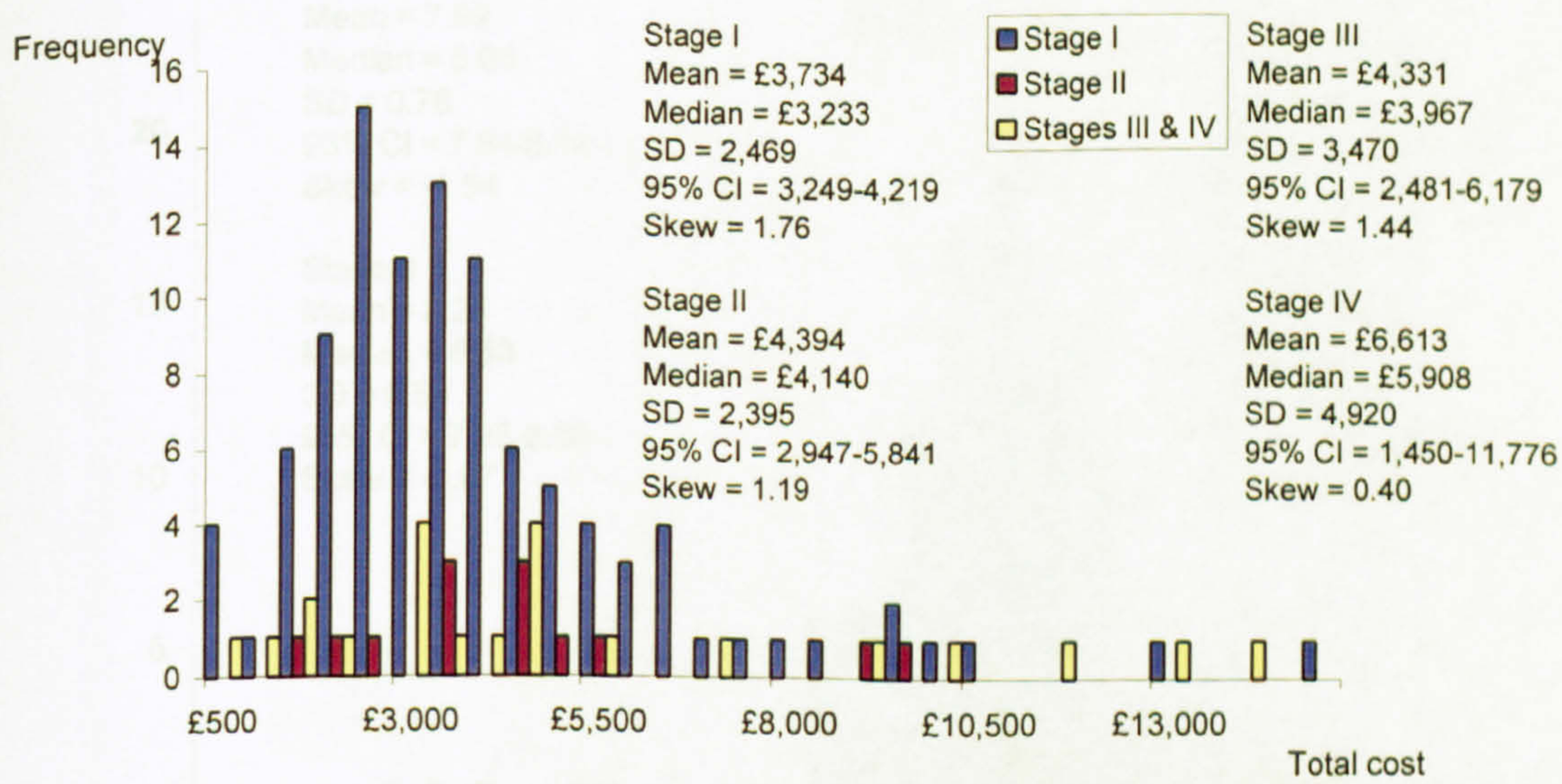


Figure 8.2 **Histogram of breast cancer cost data with outliers removed**

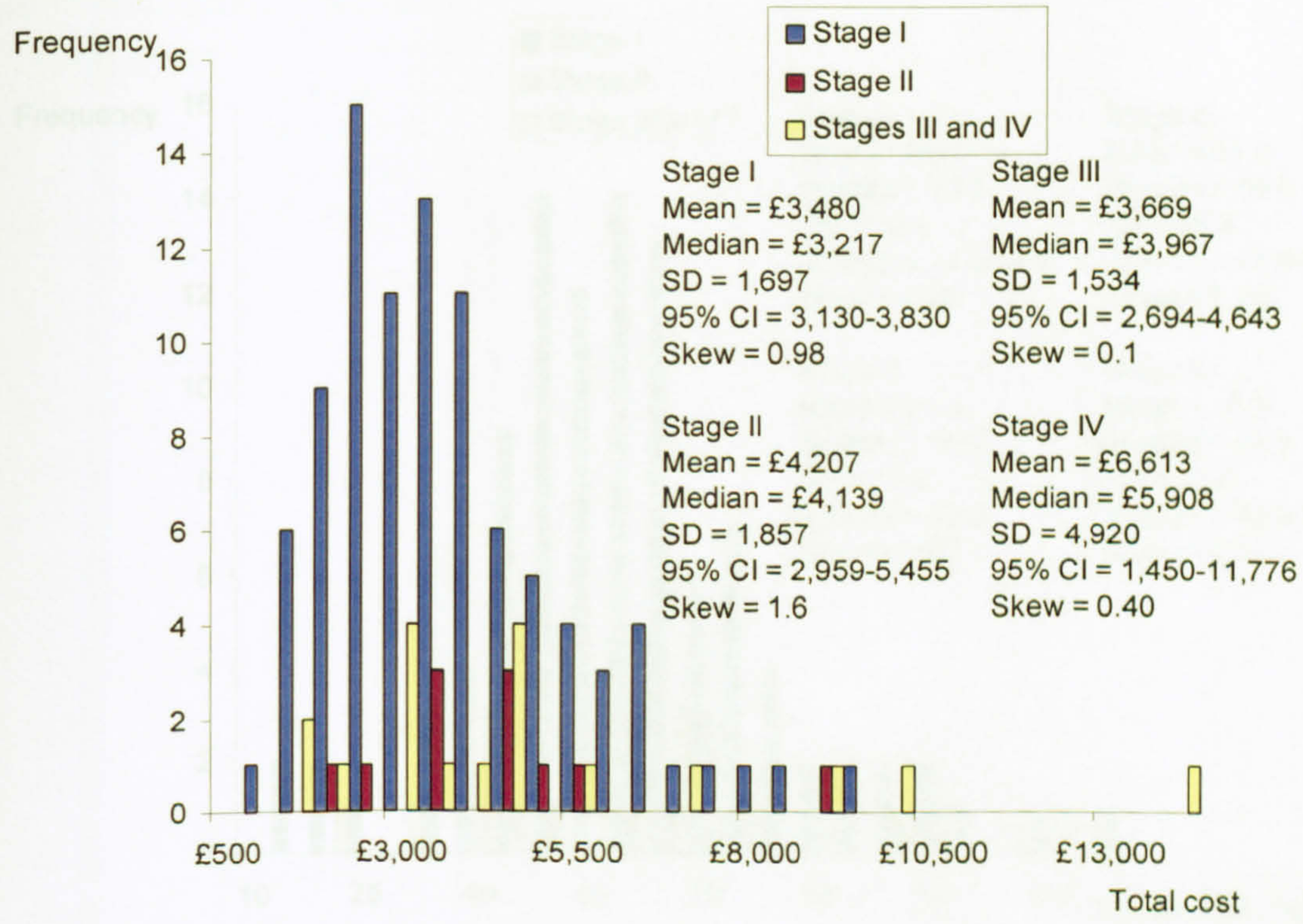


Figure 8.3 **Histogram of Ln transformed breast cancer cost data**

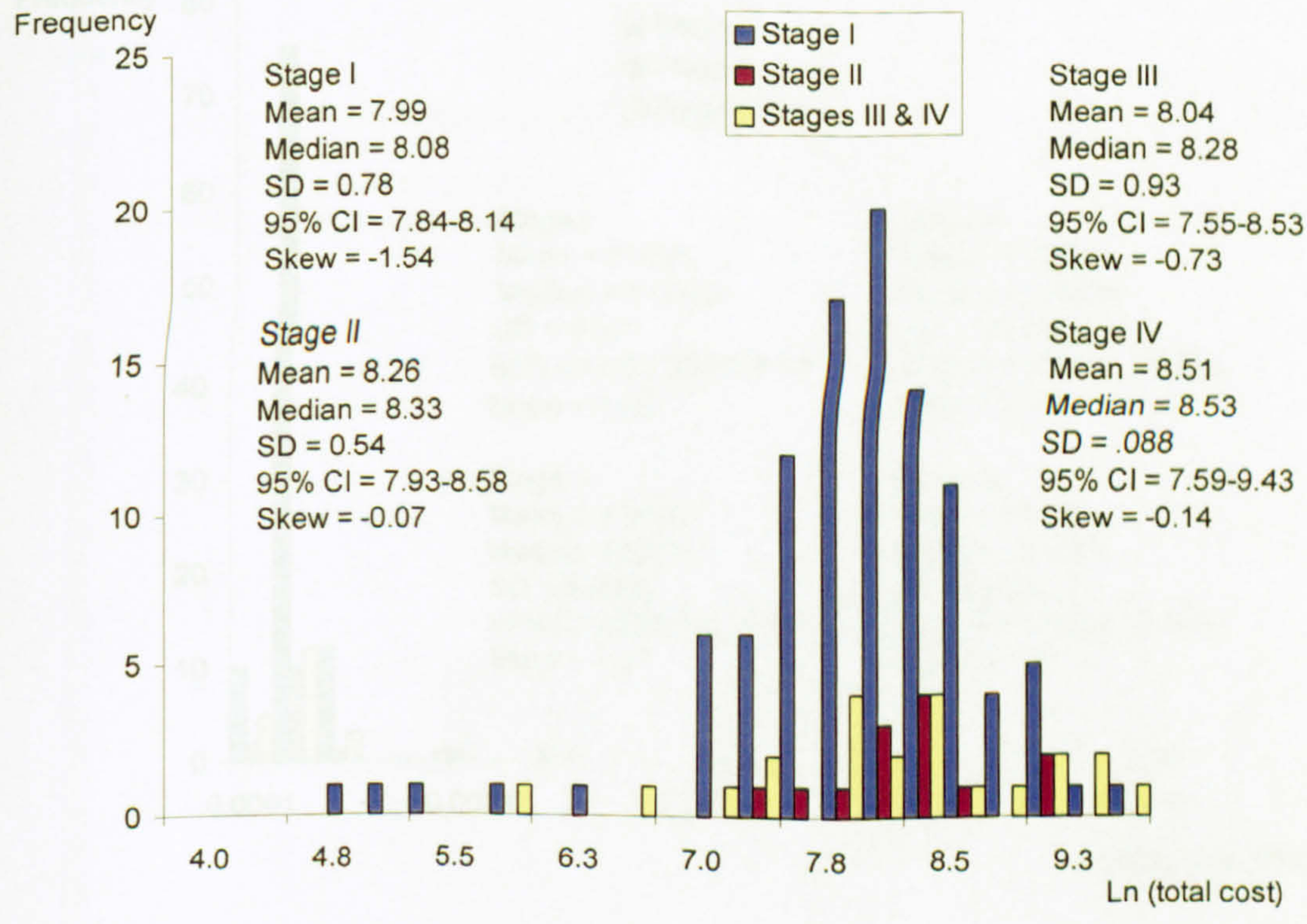


Figure 8.4 Histogram of square root transformed breast cancer cost data

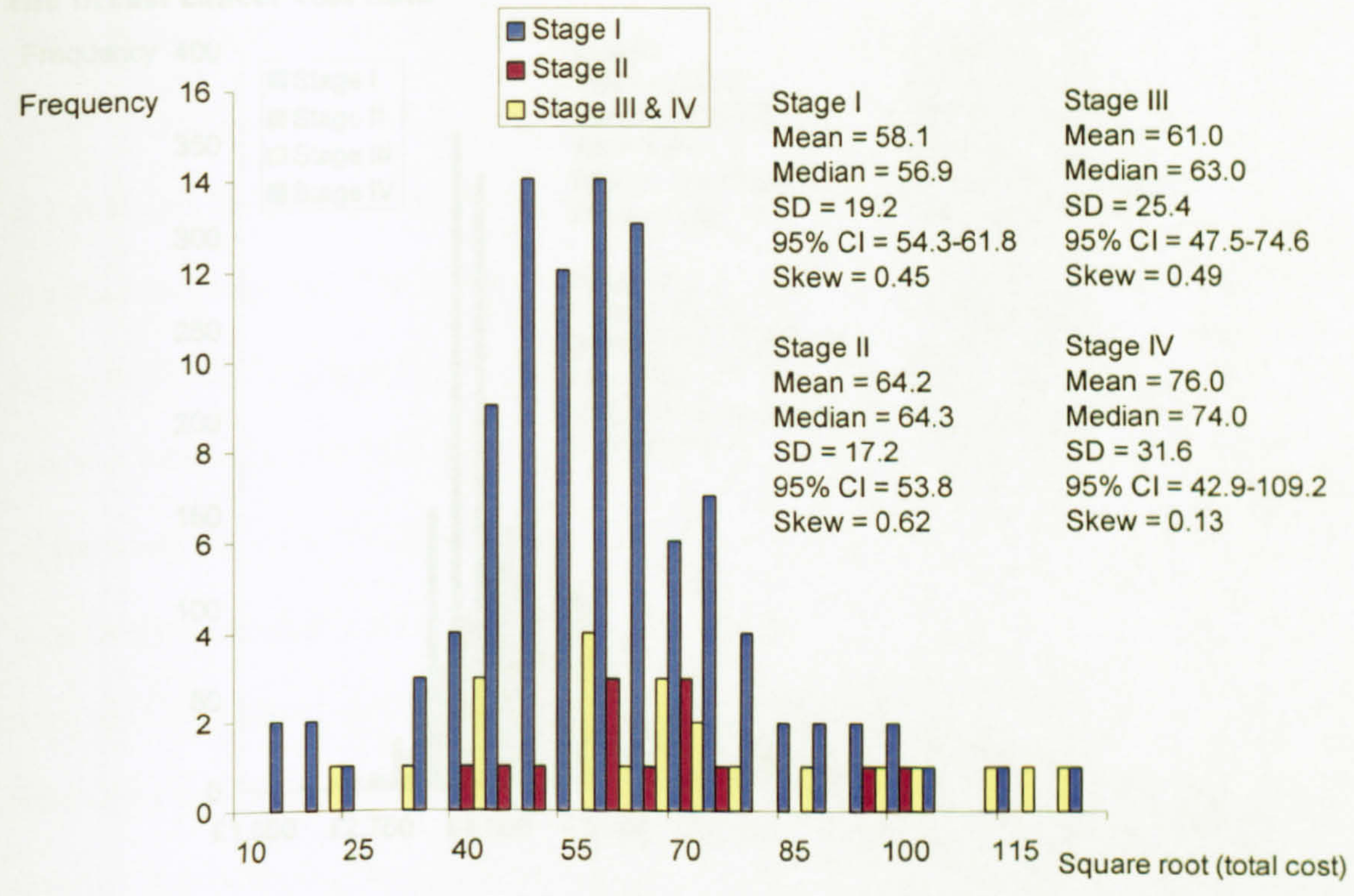


Figure 8.5 Histogram of reciprocal transformed breast cancer cost data

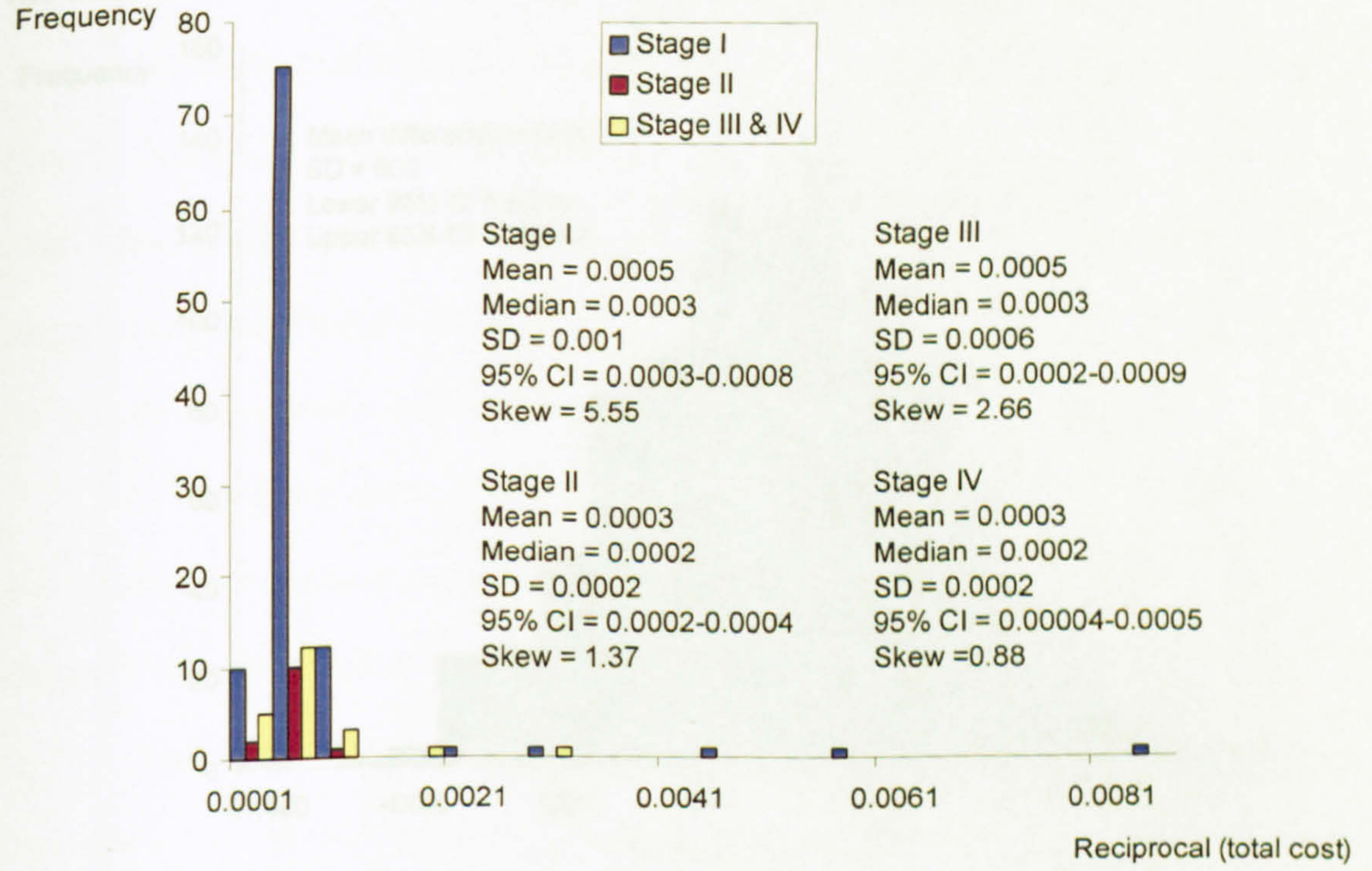


Figure 8.6 Histogram of the bootstrap estimate of the sampling distribution of the breast cancer cost data

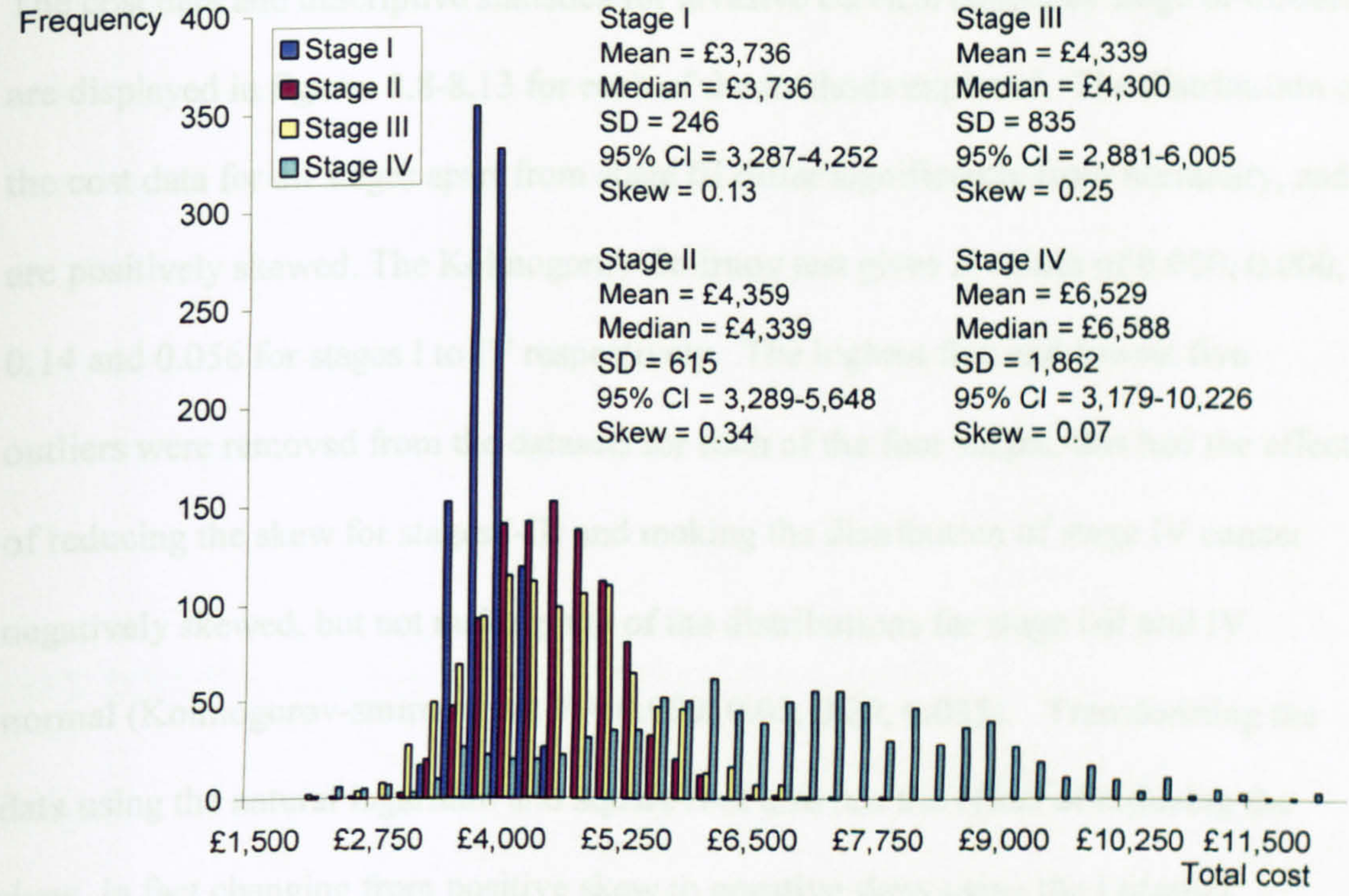
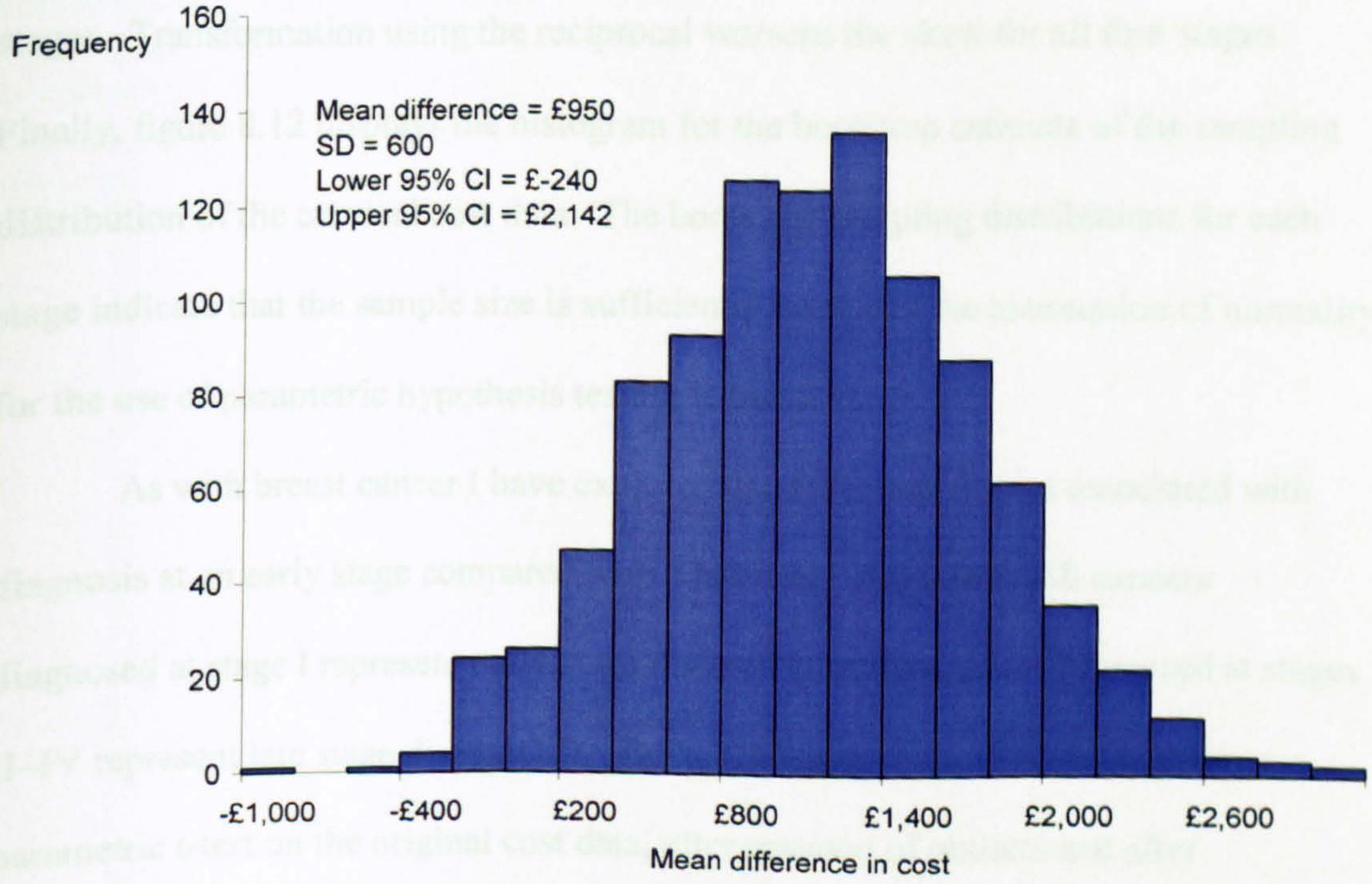


Figure 8.7 Histogram of the bootstrap estimate of the sampling distribution of the difference in costs between early and late stage breast cancer.



8.4.2 Cervical cancer

The cost data and descriptive statistics for invasive cervical cancer by stage of disease are displayed in figures 8.8-8.13 for each of the methods explored. The distribution of the cost data for all stages apart from stage III differ significantly from normality, and are positively skewed. The Kolmogorov-Smirnov test gives *P* values of 0.000, 0.000, 0.14 and 0.056 for stages I to IV respectively. The highest five and lowest five outliers were removed from the datasets for each of the four stages, this had the effect of reducing the skew for stages I-III and making the distribution of stage IV cancer negatively skewed, but not making any of the distributions for stage I-II and IV normal (Kolmogorov-smirnov test $P = 0.000, 0.01, 0.20, 0.035$). Transforming the data using the natural logarithm and square root also has the effect of reducing the skew, in fact changing from positive skew to negative skew using the Ln(cost), transforming the data also has the effect of equalising the variances between the stages. Transformation using the reciprocal worsens the skew for all four stages. Finally, figure 8.12 displays the histogram for the bootstrap estimate of the sampling distribution of the cervical cost data. The bootstrap sampling distributions for each stage indicate that the sample size is sufficiently large that the assumption of normality for the use of parametric hypothesis testing is justified.

As with breast cancer I have explored the difference in cost associated with diagnosis at an early stage compared with a late stage diagnosis. All cancers diagnosed at stage I represent early stage disease, whereas cancers diagnosed at stages II–IV represent late stage disease(17). Table 8.2 displays the results using the parametric t-test on the original cost data, after removal of outliers and after

transforming the data, to explore the difference between early and late stage cancer. All methods suggest a significant difference in costs between cancers diagnosed at an early stage compared to those diagnosed at a later stage. The bootstrap estimate of the sampling distribution of the mean cost difference was found to be significant at £4,309, with a standard deviation around this mean of 843(this standard deviation is equivalent to the standard error of the mean difference using parametric statistics), and 95 % confidence intervals ranging from £2,715-£5,971(see Figure 8.14).

Table 8.2 Results of parametric and nonparametric analysis of difference in early stage and late stage costs – Invasive cervical cancer

Data	Stage	N	Mean	SD	Mean difference	Test statistic	P value	Skew
Original	Early	128	6,622	4,753	4,339	4.93	0.000	2.01
	Late	132	10,959	8,797				2.41
Outliers removed	Early	118	6,196	3,371	3,546	6.30	0.000	1.03
	Late	102	9,741	4,920				0.91
Ln transformed	Early	128	8.56	0.77	0.42	3.99	0.00	-1.78
	Late	132	8.98	0.92				-1.51
Square root transformed	Early	128	77.04	26.28	20.52	5.04	0.00	0.84
	Late	132	97.56	38.10				0.69
Mann Whitney							0.000	

Figure 8.8 Histogram of original cervical cancer cost data by stage

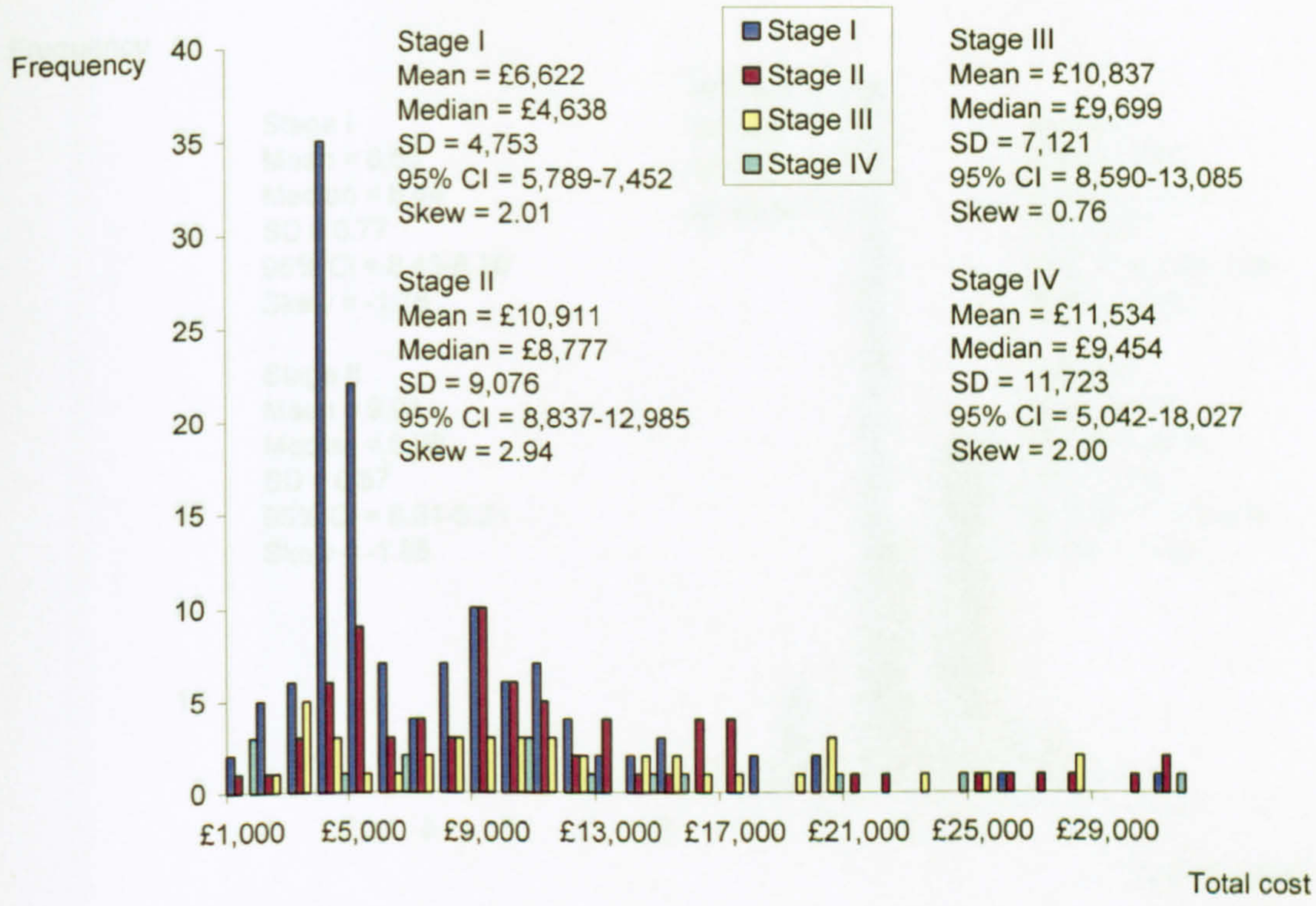


Figure 8.9 Histogram of cervical cost data with outliers removed

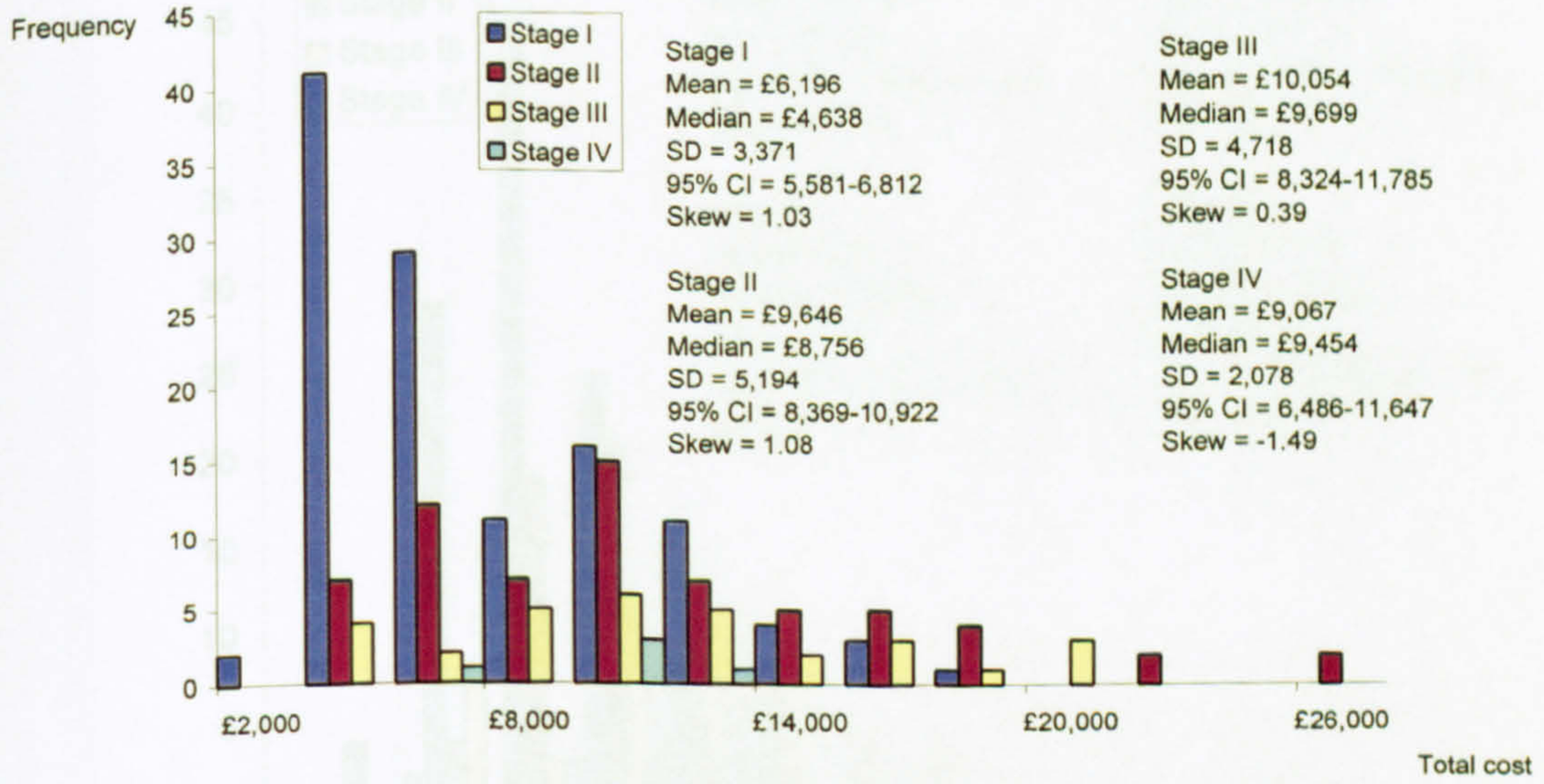


Figure 8.10 Histogram of Ln transformed cervical cost data

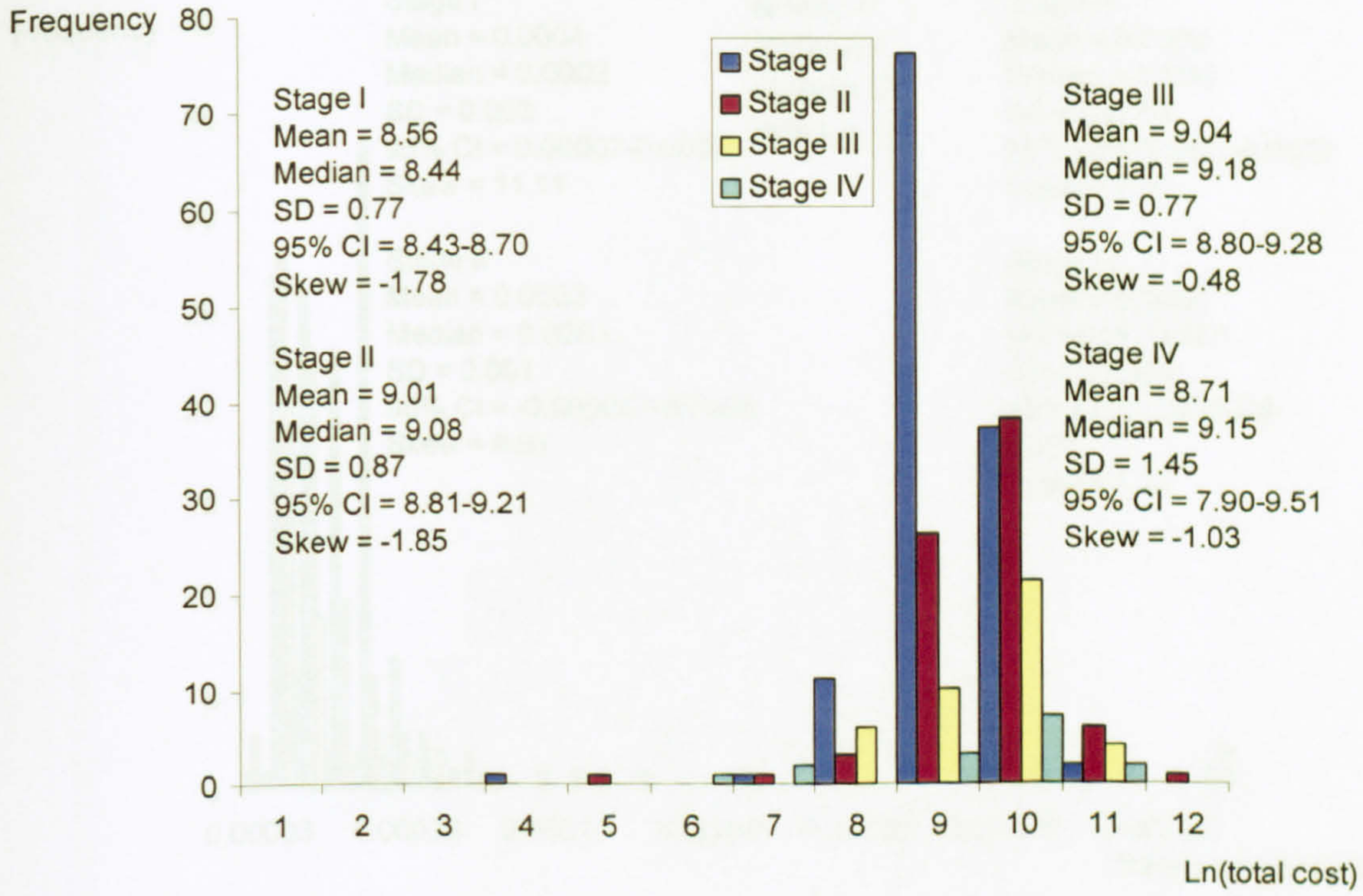


Figure 8.11 Histogram of square root transformed cervical cost data

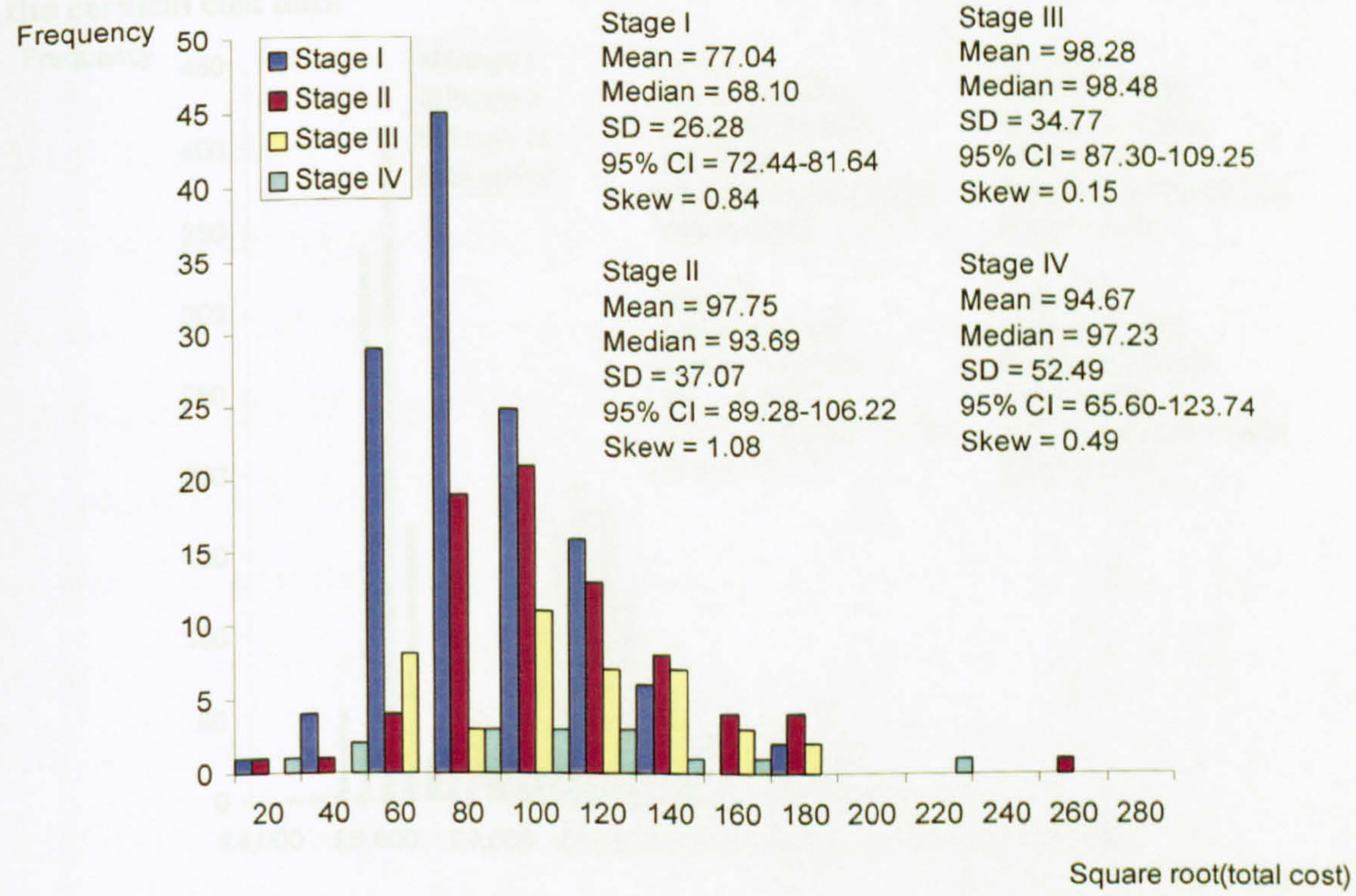


Figure 8.12 Histogram of reciprocal transformed cervical cost data

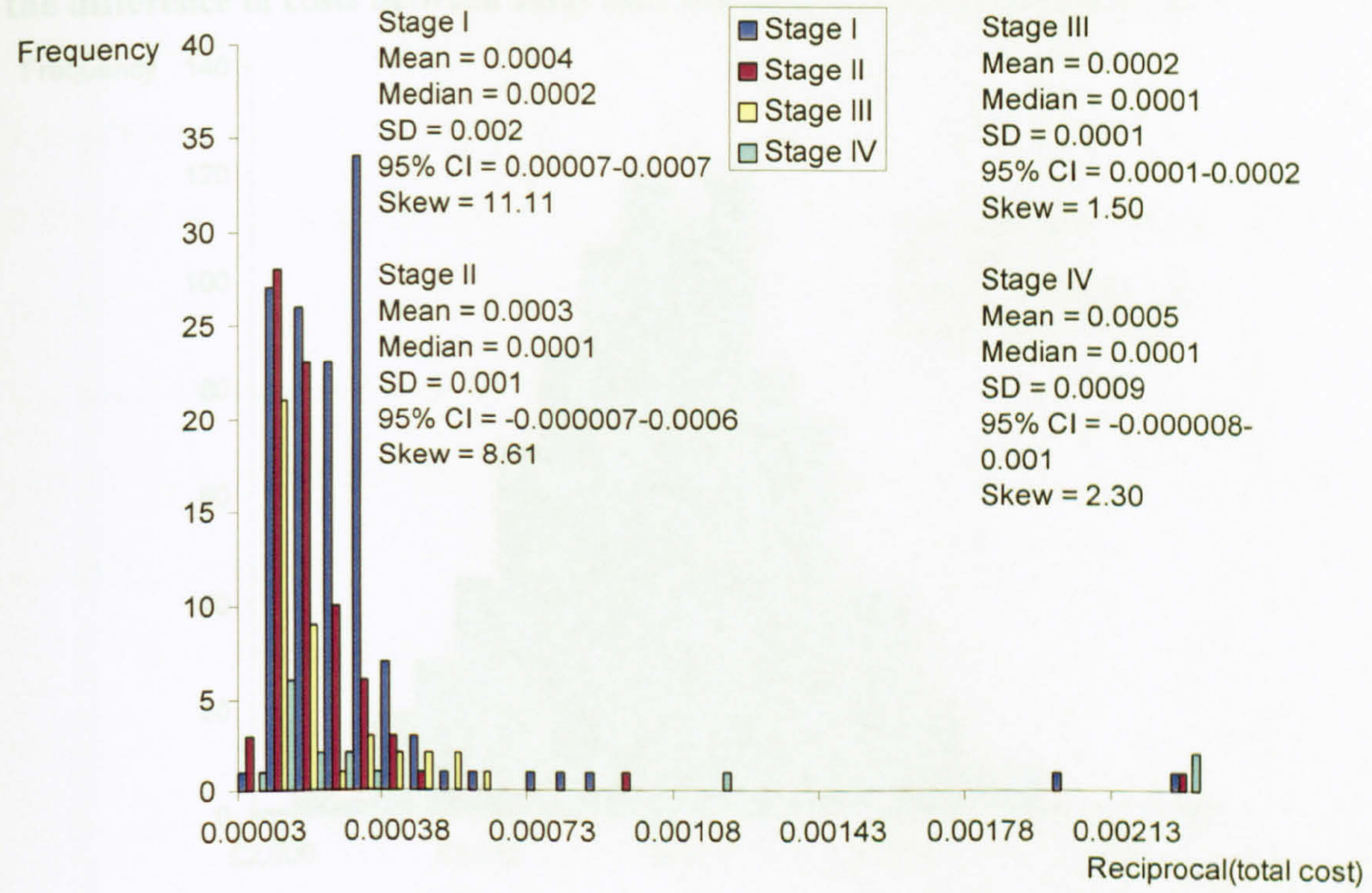


Figure 8.13 Histogram of the bootstrap estimate of the sampling distribution of the cervical cost data

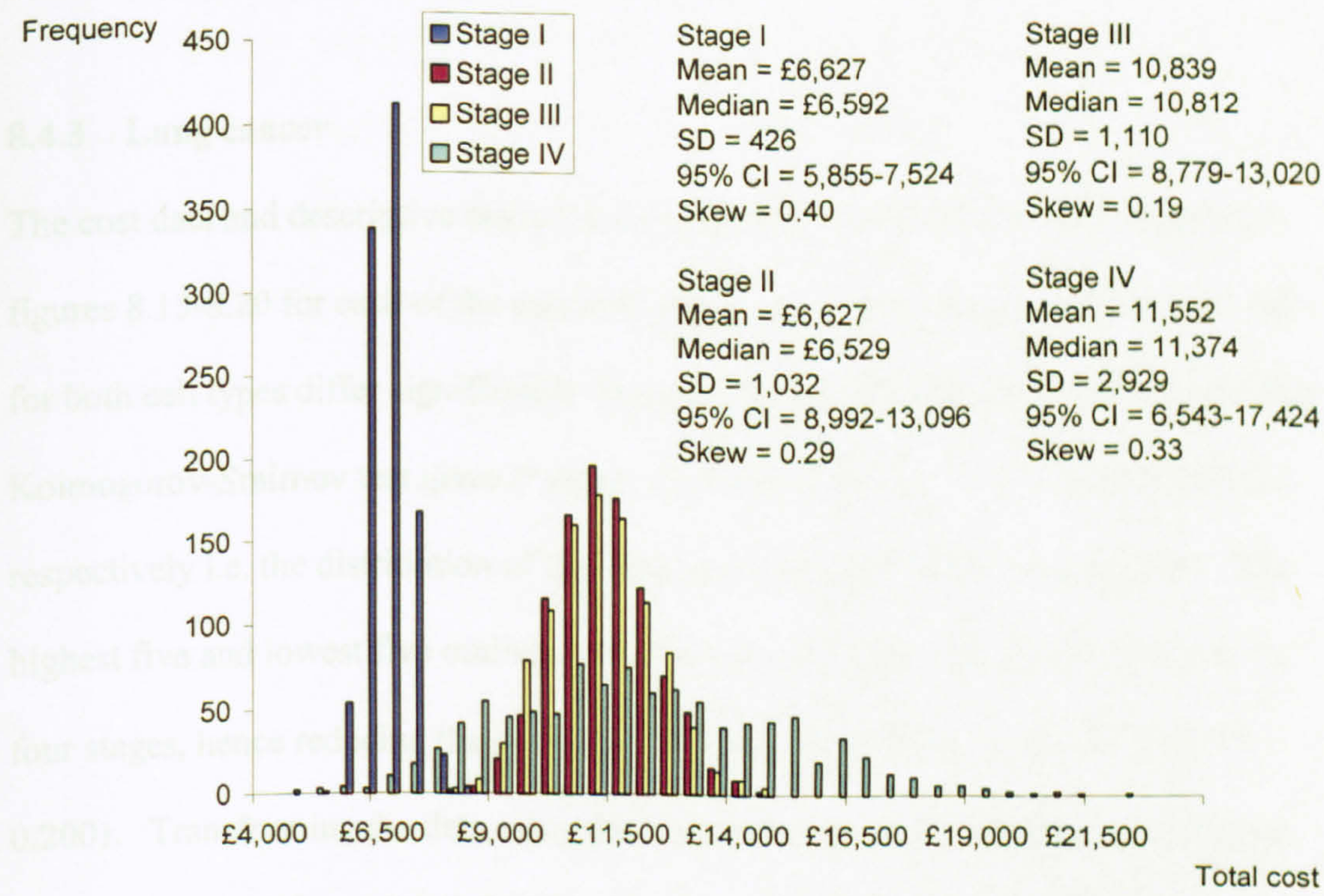
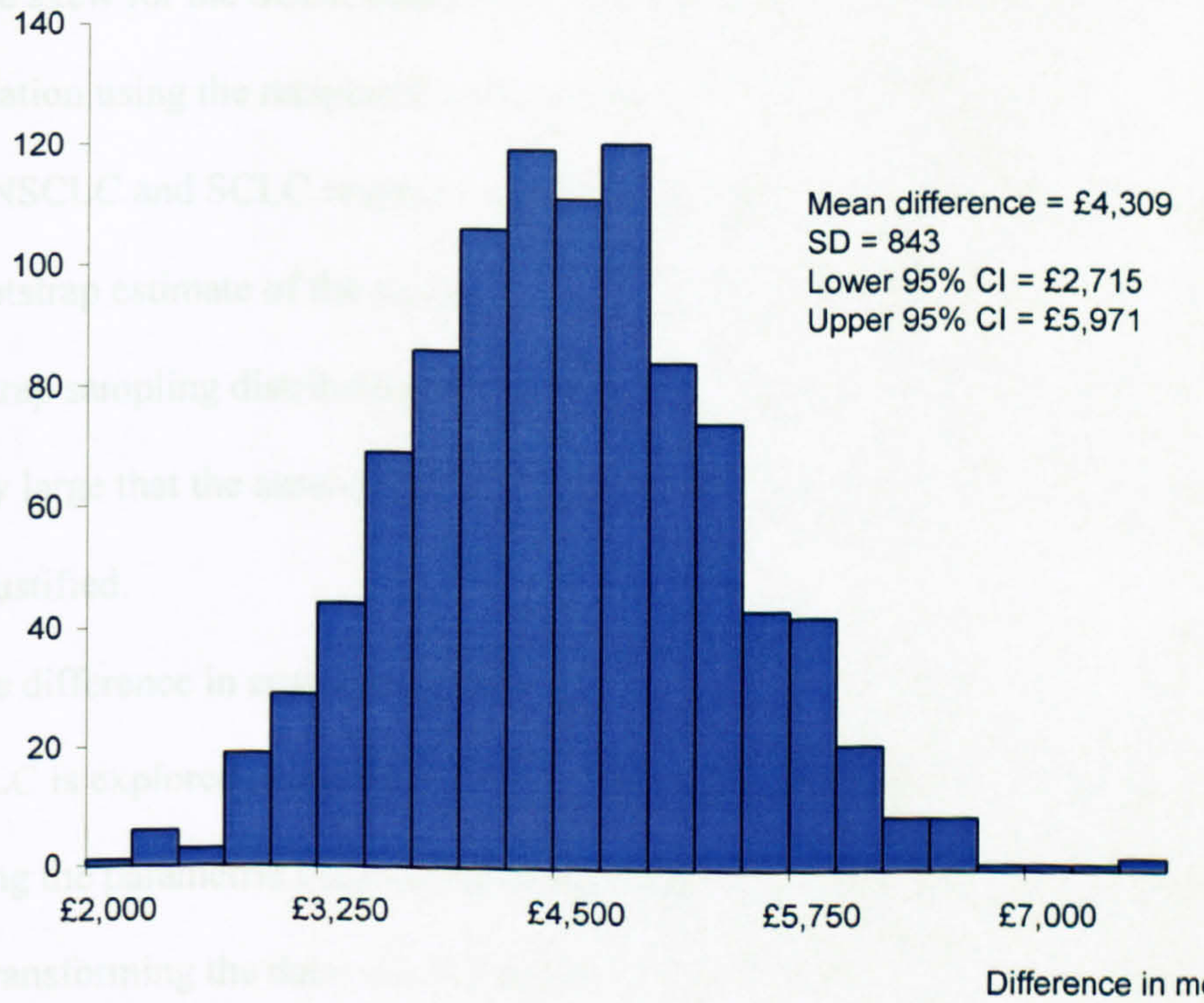


Figure 8.14 Histogram of the bootstrap estimate of the sampling distribution of the difference in costs between early and late stage invasive cervical cancer



8.4.3 Lung cancer

The cost data and descriptive statistics for lung cancer by cell type are displayed in figures 8.15-8.20 for each of the methods explored. The distribution of the cost data for both cell types differ significantly from normality, and are positively skewed. The Kolmogorov-Smirnov test gives *P* values of 0.000 and 0.04, for NSCLC and SCLC respectively i.e. the distribution of the data significantly differ from normality. The highest five and lowest five outliers were removed from the datasets for each of the four stages, hence reducing the skew, but only significantly for the SCLC data (P = 0.200). Transforming the data using the square root also has the effect of reducing the skew, (P = 0.07 and 0.165 for NSCLC and SCLC respectively using the

Kolmogorov-Smirnov test). Whereas, transformation using the natural logarithm only reduced the skew for the SCLC data ($P = 0.20$), but not the NSCLC data ($P = 0.000$). Transformation using the reciprocal worsens the skew for both datasets ($P = 0.000$ and 0.016 for NSCLC and SCLC respectively). Finally, figure 8.12 displays the histogram for the bootstrap estimate of the sampling distribution of the lung cancer cost data. The bootstrap sampling distributions for each cell type indicate that the sample size is sufficiently large that the assumption of normality for the use of parametric hypothesis testing is justified.

The difference in cost associated with being diagnosed as SCLC compared with NSCLC is explored using the various methods of analysis. Table 8.3 displays the results using the parametric t-test on the original cost data, after removal of outliers and after transforming the data, and the nonparametric Mann-Whitney test to explore the difference between early and late stage cancer. All methods suggest no significant difference in costs between cancers diagnosed as being the non-small cell type compared with the small cell type. The bootstrap estimate of the sampling distribution of the mean cost difference of £475 was also found to be non-significant, with a standard deviation around this mean of 971(this standard deviation is equivalent to the standard error of the mean difference using parametric statistics), and 95 % confidence intervals ranging from £ -1,495-£2,299 (see Figure 8.21).

Table 8.3 Results of parametric analysis of difference in NSCLC and SCLC costs

Data	Stage	N	Mean	SD	Mean difference	Test statistic	P value	Skew
Original	NSCLC	227	6,150	7,333	482	0.328	0.743	4.86
	SCLC	26	5,668	4,426				0.74
Outliers removed	NSCLC	217	5,563	4,738	704	0.586	0.559	1.13
	SCLC	16	4,858	2,919				1.26
Ln transformed	NSCLC	227	8.10	1.34	0.20	0.745	0.457	-1.25
	SCLC	26	8.30	0.89				-1.74
Square root transformed	NSCLC	227	68.81	37.71	0.92	0.101	0.920	1.09
	SCLC	26	69.58	29.32				0.37
Mann Whitney							0.775	

Figure 8.15 Histogram of original cost data for lung cancer by cell type

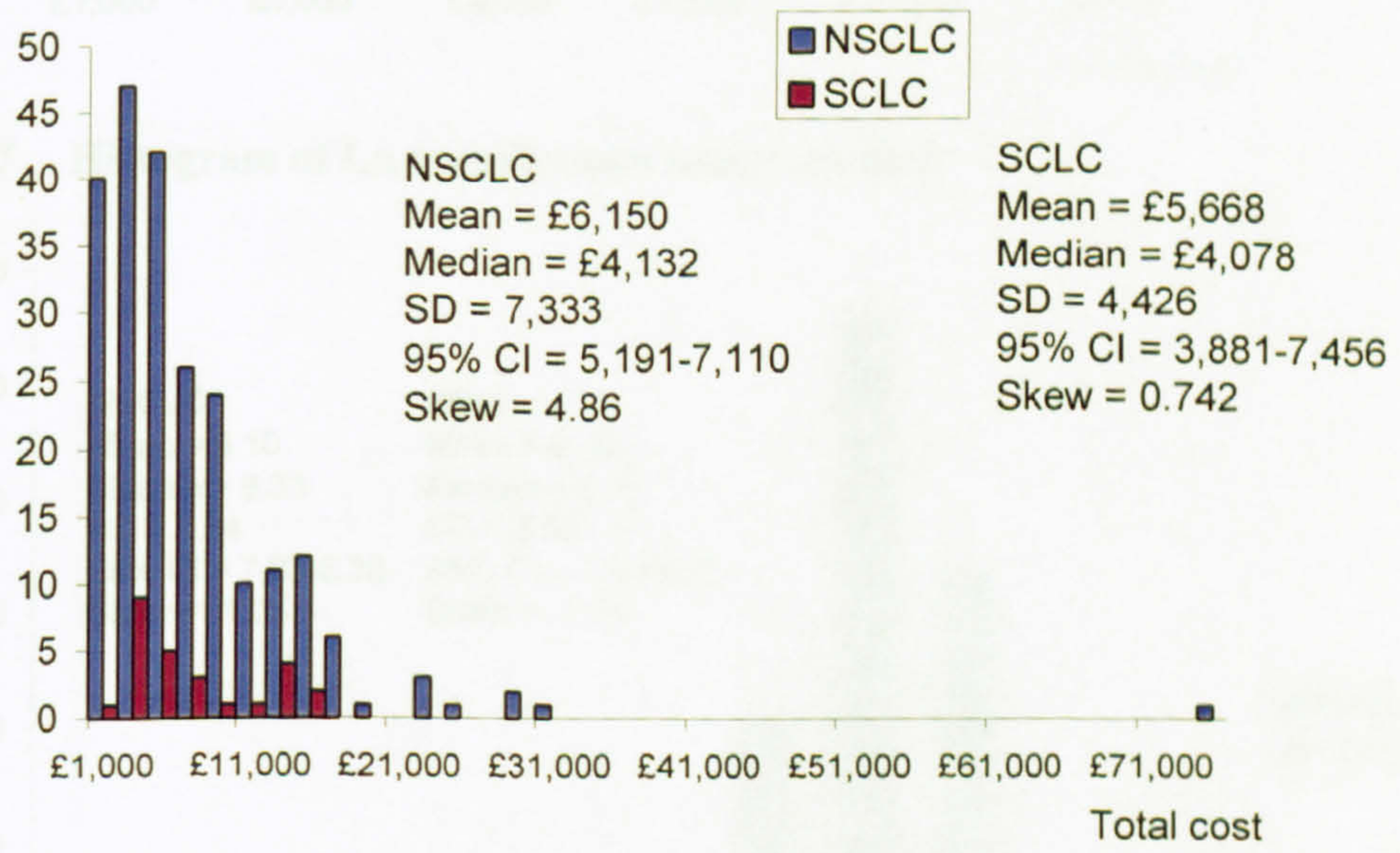


Figure 8.16 Histogram of lung cost data with outliers removed

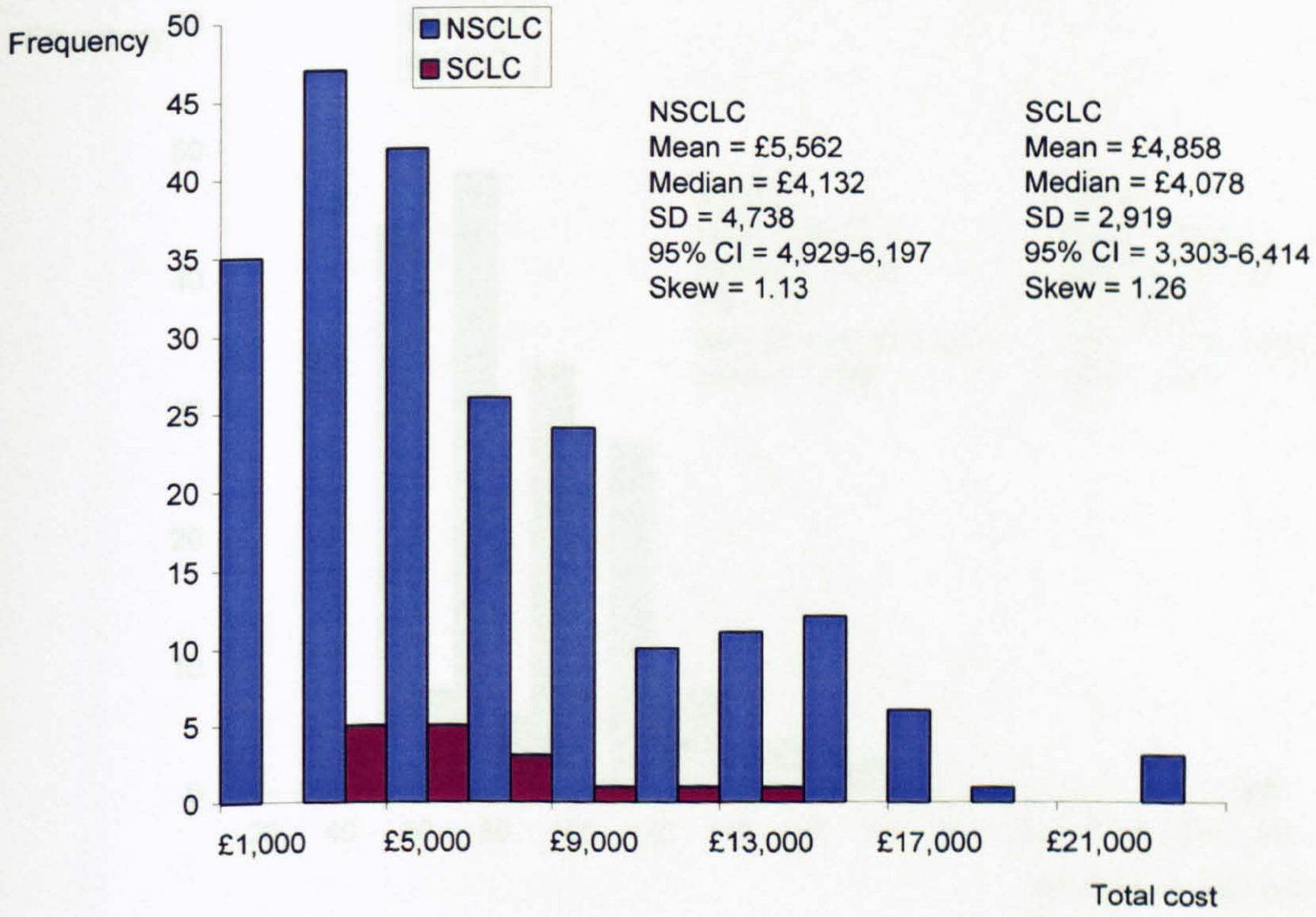


Figure 8.17 Histogram of Ln transformed lung cost data

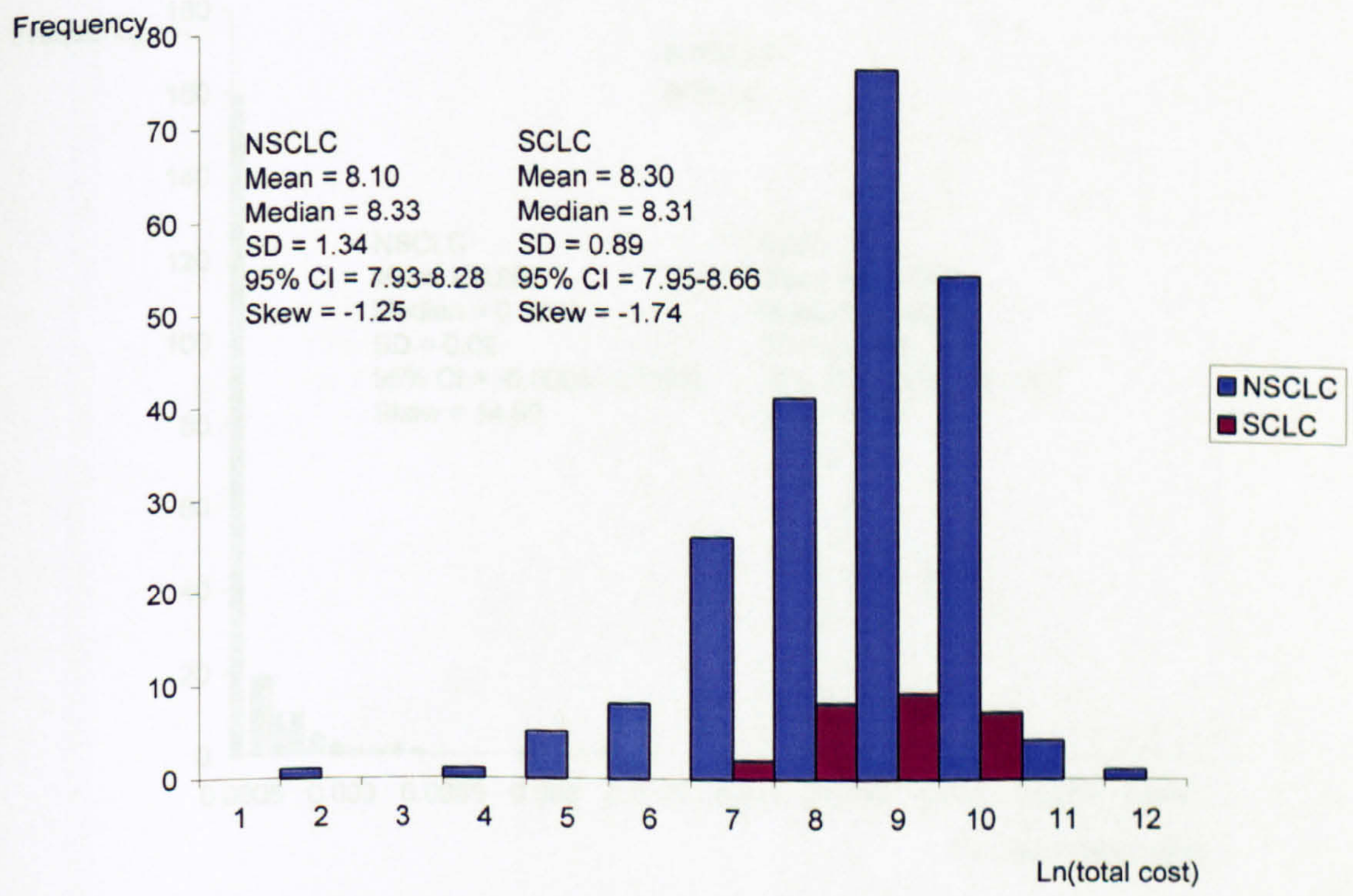


Figure 8.18 Histogram of square root transformed lung cost data

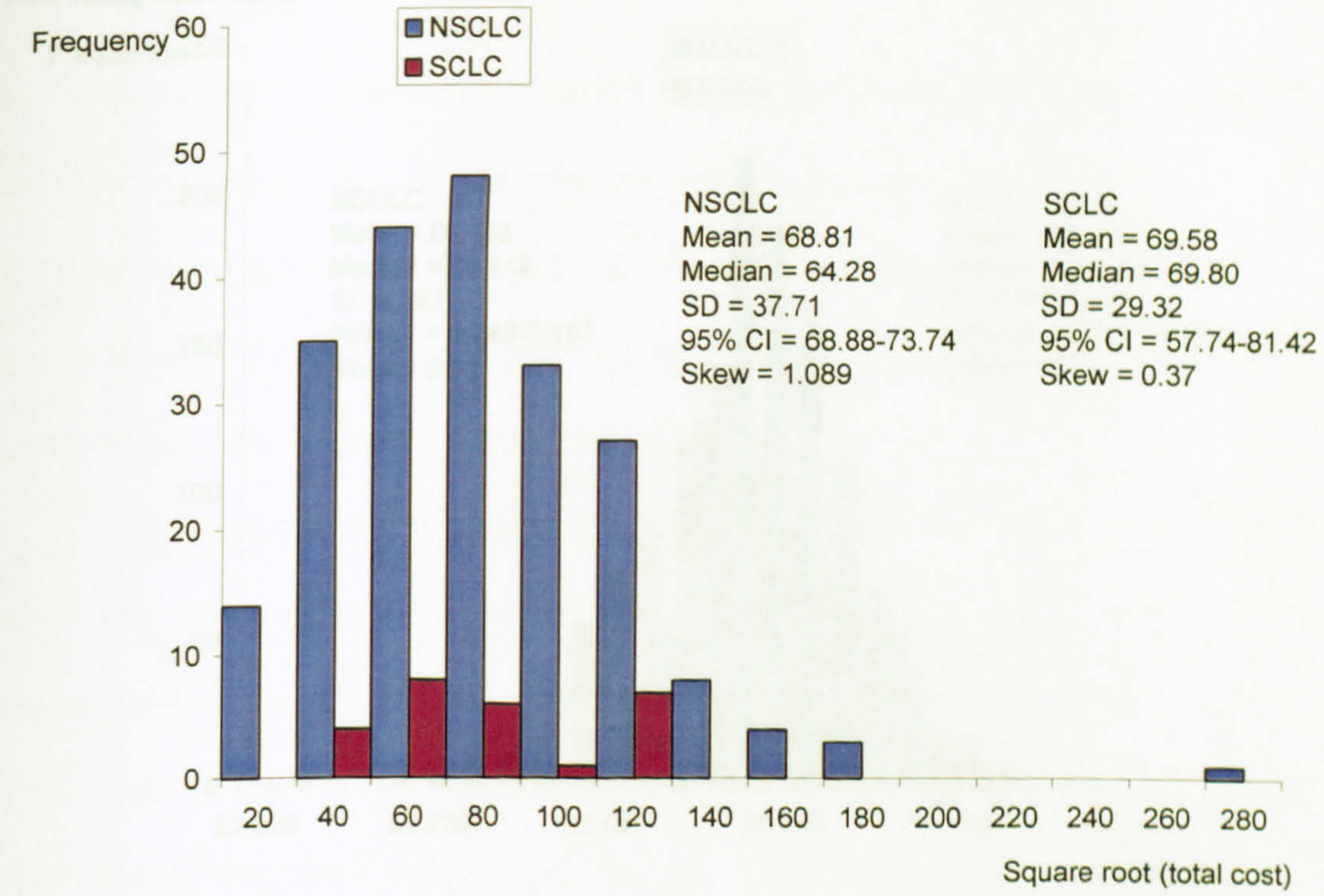


Figure 8.19 Histogram of reciprocal transformed lung cost data

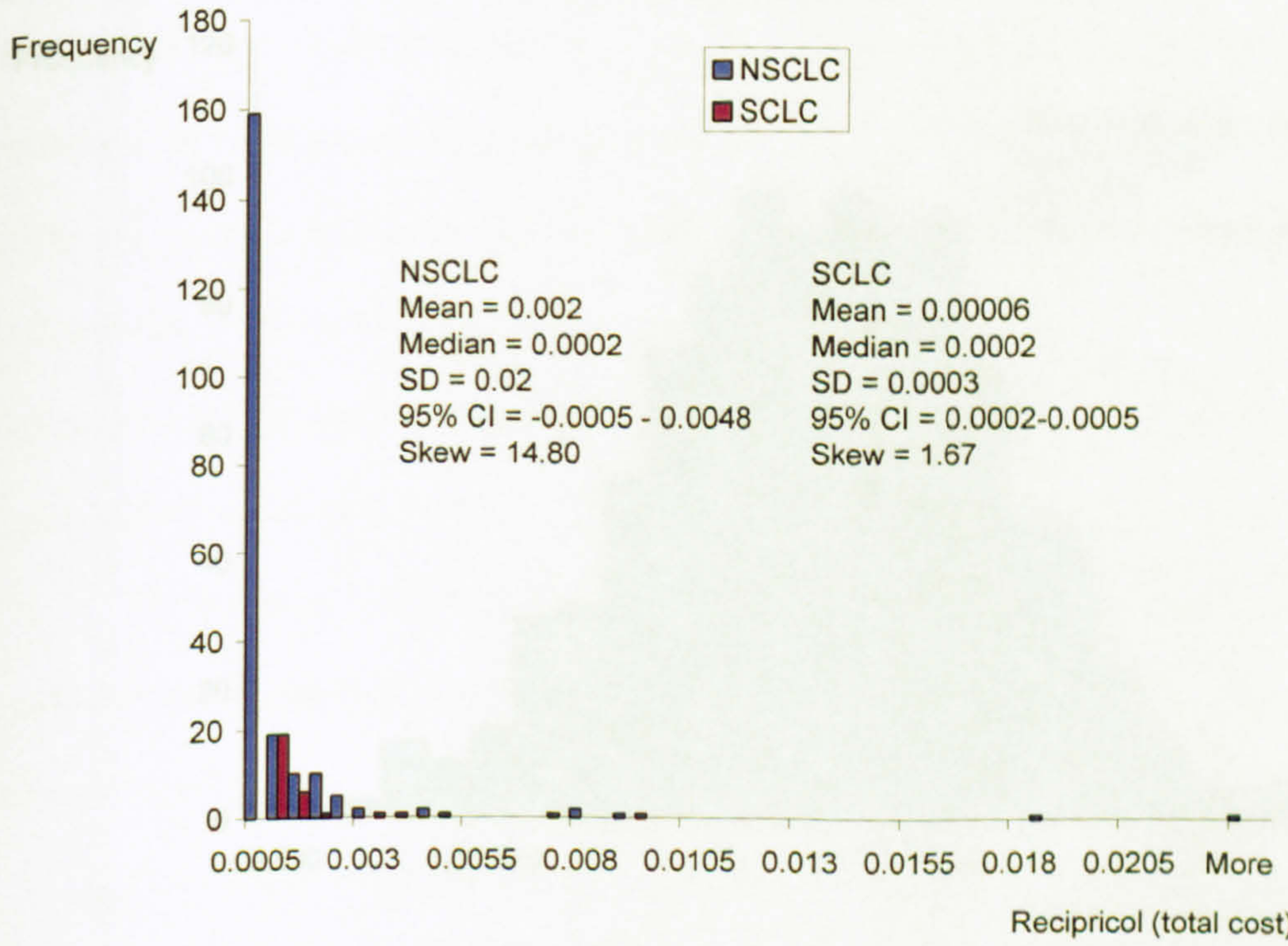


Figure 8.20 Histogram of the bootstrap estimate of the sampling distribution of the lung cost data

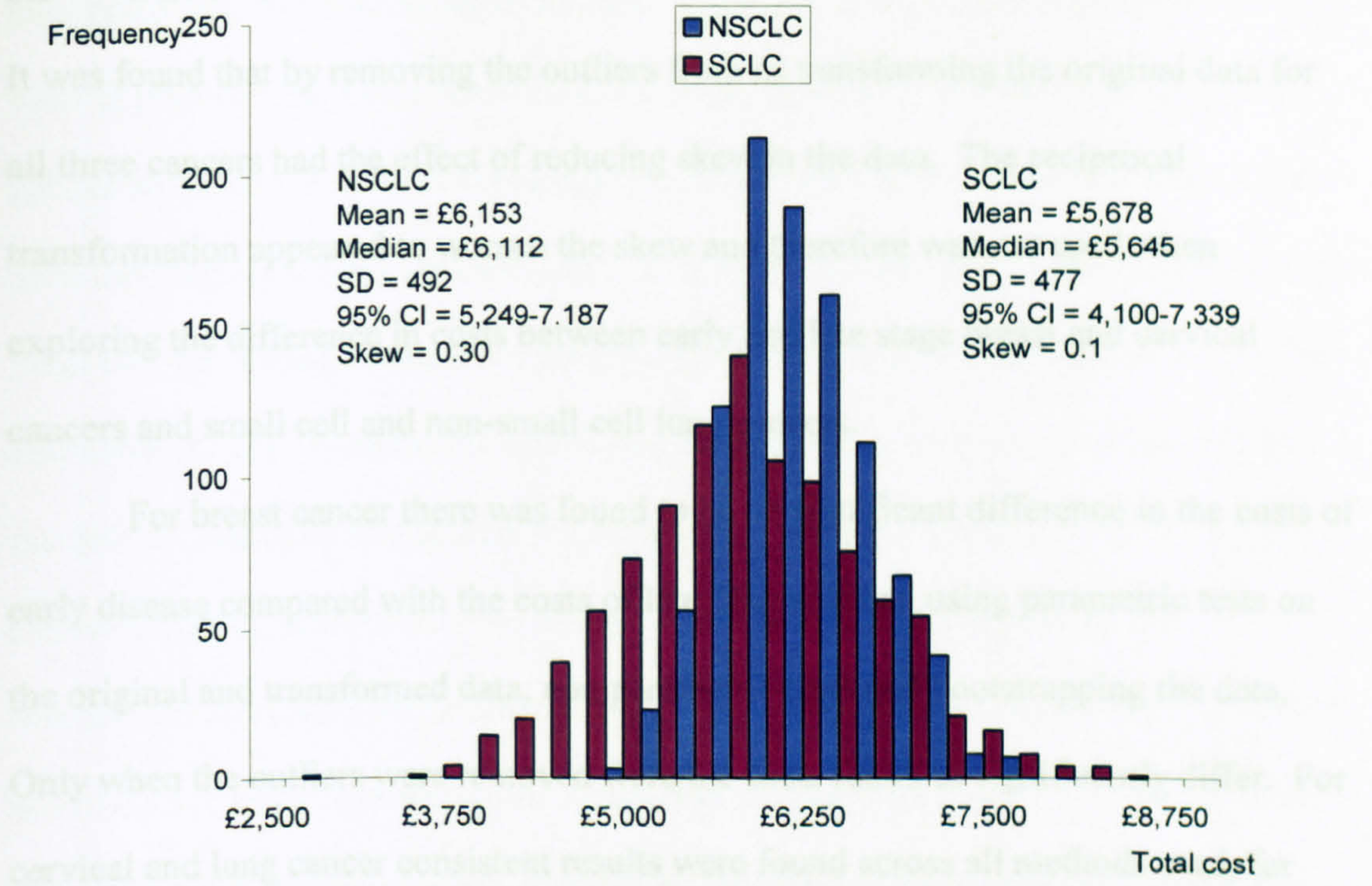
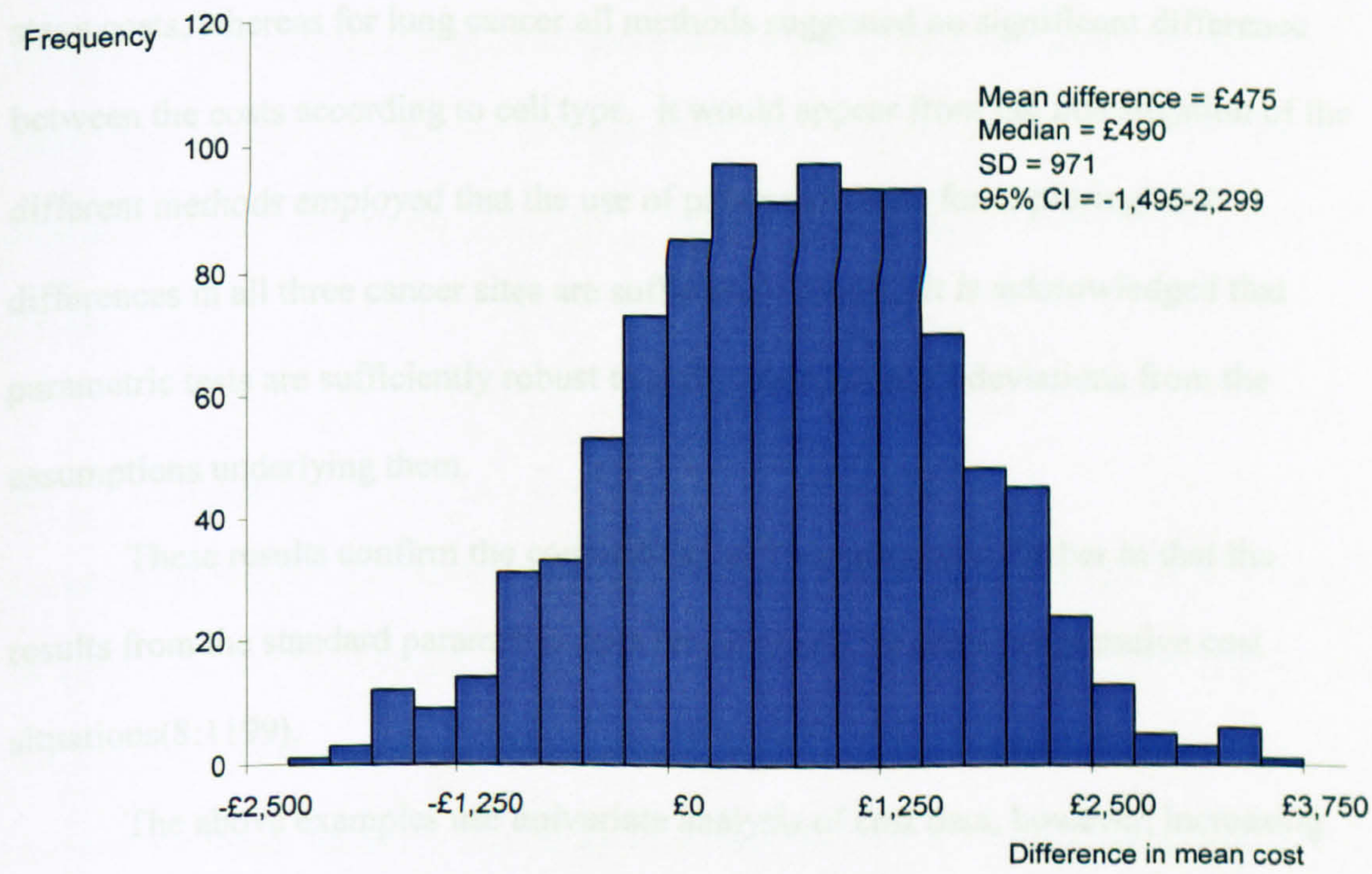


Figure 8.21 Histogram of the bootstrap estimate of the sampling distribution of the difference in costs between NSCLC and SCLC



8.5 Discussion

It was found that by removing the outliers from or transforming the original data for all three cancers had the effect of reducing skew in the data. The reciprocal transformation appeared to worsen the skew and therefore was not used when exploring the difference in costs between early and late stage breast and cervical cancers and small cell and non-small cell lung cancers.

For breast cancer there was found to be no significant difference in the costs of early disease compared with the costs of late disease when using parametric tests on the original and transformed data, non parametric tests and bootstrapping the data. Only when the outliers were removed were the costs found to significantly differ. For cervical and lung cancer consistent results were found across all methods used, for cervical cancer all methods suggested a significant difference between early and late stage costs, whereas for lung cancer all methods suggested no significant difference between the costs according to cell type. It would appear from the investigation of the different methods employed that the use of parametric tests for exploring cost differences in all three cancer sites are sufficiently robust. It is acknowledged that parametric tests are sufficiently robust to accommodate small deviations from the assumptions underlying them.

These results confirm the conclusions of Thompson and Barber in that the results from the standard parametric tests are adequate for most comparative cost situations(8:1199).

The above examples use univariate analysis of cost data, however, increasing use of multivariate analysis of cost data is being undertaken. Potential multivariate

analysis includes ordinary least squares regression (OLS), and parametric and non-parametric survival (failure-time) models. Ordinary least squares regression has been used to predict costs while controlling for covariables such as disease severity, age, gender etc. Two UK studies exploring the costs of colorectal cancer and mental health used the OLS regression to determine whether health economists could predict ex-ante what cost-generating events have the greatest impact on cost and therefore should be collected(18, 19). Whereas the underlying assumption of univariate analyses is that the data are normally distributed, the assumption underlying OLS is that the error terms from the predicted data are normally distributed. OLS regression on transformed data and non-parametric survival methods such as Kaplan-Meier survival analysis have been used where this assumption is violated. The Kaplan-Meier method also allows for analysis of costs where data are missing due to attrition (also known as drop-out or censoring) in longitudinal studies (the use of this method is explored in chapter 9). The relative merits of several multivariate methods for analysing cost data have been explored by a few researchers. However, as with the analysis of univariate cost data no firm conclusion as to the most appropriate method has been reached(1, 13, 20).

8.6 Conclusions

Given the requirement of health economists to compare patient groups in terms of the arithmetic mean costs, standard parametric approaches to hypothesis testing such as use of the t-test and one-way analysis of variance seem appropriate. However, the problem for health economists in using such tests lie in their assumptions of the

normality of the distribution of the data. Cost data are invariably positively skewed resulting in a violation of the assumption of normality and according to standard statistics restricting the use of parametric tests. This chapter has explored the use of alternative methods for the univariate analysis of cost data, although these have their own problems for use by health economists. Removal of outliers may well reduce the skew but also distorts any information on the total budget required for treating a particular group, by removing potentially important information. Use of transformed cost data also has the effect of reducing the skew of the data and additionally equalises the variances allowing the use of parametric tests, however there is a problem with interpretation of transformed means, standard deviations and confidence intervals. Health economists and policy makers require the information on the original scale, the cost scale. Back-transformation of the results from reciprocal and square root transformed data are meaningless, and although back-transformation using the exponential on natural logged cost data is possible, the process gives a geometric rather than arithmetic mean. Use of non-parametric tests also suffers from the lack of appropriate information to enable the calculation of a cost-effectiveness ratio. The bootstrap method is able to deal appropriately with skewed data, and can be used to report a measure of central tendency and confidence intervals around the mean. It can also be used as a check on the normality assumption of the sampling distribution of the data being analysed.

From this chapter it can be concluded that:

- Reporting of the distributional form of the data being analysed is of paramount importance. This can be done using descriptive statistics such as the mean,

standard deviation and confidence intervals and a visual representation of the distribution using a histogram of costs or a scatter plot of cost and effect pairs. Reporting of the median and quartiles alongside the mean and standard devaition are useful when the distribution is skewed.

- The arithmetic mean value should always be reported, even where data are skewed, as this is the value health economists require to calculate cost-effectiveness ratios and is also a necessary requirement for the estimation of the total cost involved in providing packages of care or implementing treatments.
- Use of parametric hypothesis tests for exploring comparisons in arithmetic means are usually justified as long as the results are accompanied by descriptive information about the data.
- Where skewed data are a problem the bootstrap method can be used to estimate confidence intervals around a mean estimate of the difference in sampling distributions.
- The bootstrap method can also be used as a check on the assumptions for using parametric methods.
- It is acknowledged that parametric tests are sufficiently robust to accommodate small deviations from the assumptions underlying them.

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Chapter 9

Estimating costs with censored data

9.1 Introduction

The previous chapters have explored the costs involved with diagnosis, treatment and follow-up for breast, cervical and lung cancer patients. Observed counts of separate categories of patient-level resource use data were weighted by unit cost information and summed to provide an estimate of per patient total cost. This enabled comparisons of the average per patient costs according to disease severity (stage or cell type) to be made by dividing the total cost per patient by the total number of patients in each group. However, this method assumes that there is full cost information for all patients across all time periods in the study. Ideally, medical cost data should be available from diagnosis or implementation of an intervention until a specified time of follow up (or death if occurring before the specified period of follow up). This specified time of follow up should include all cost-generating events related to the disease or intervention being investigated i.e. all attributable costs.

Figure 9.1 displays this idea graphically, the period beyond time t is the phase beyond which it becomes difficult to attribute costs to the specific disease or intervention as the patients are considered cured. The population on average incurs a baseline cost of medical care, as health economists we are interested in the additional cost incurred by the disease or intervention being examined. For certain diseases such

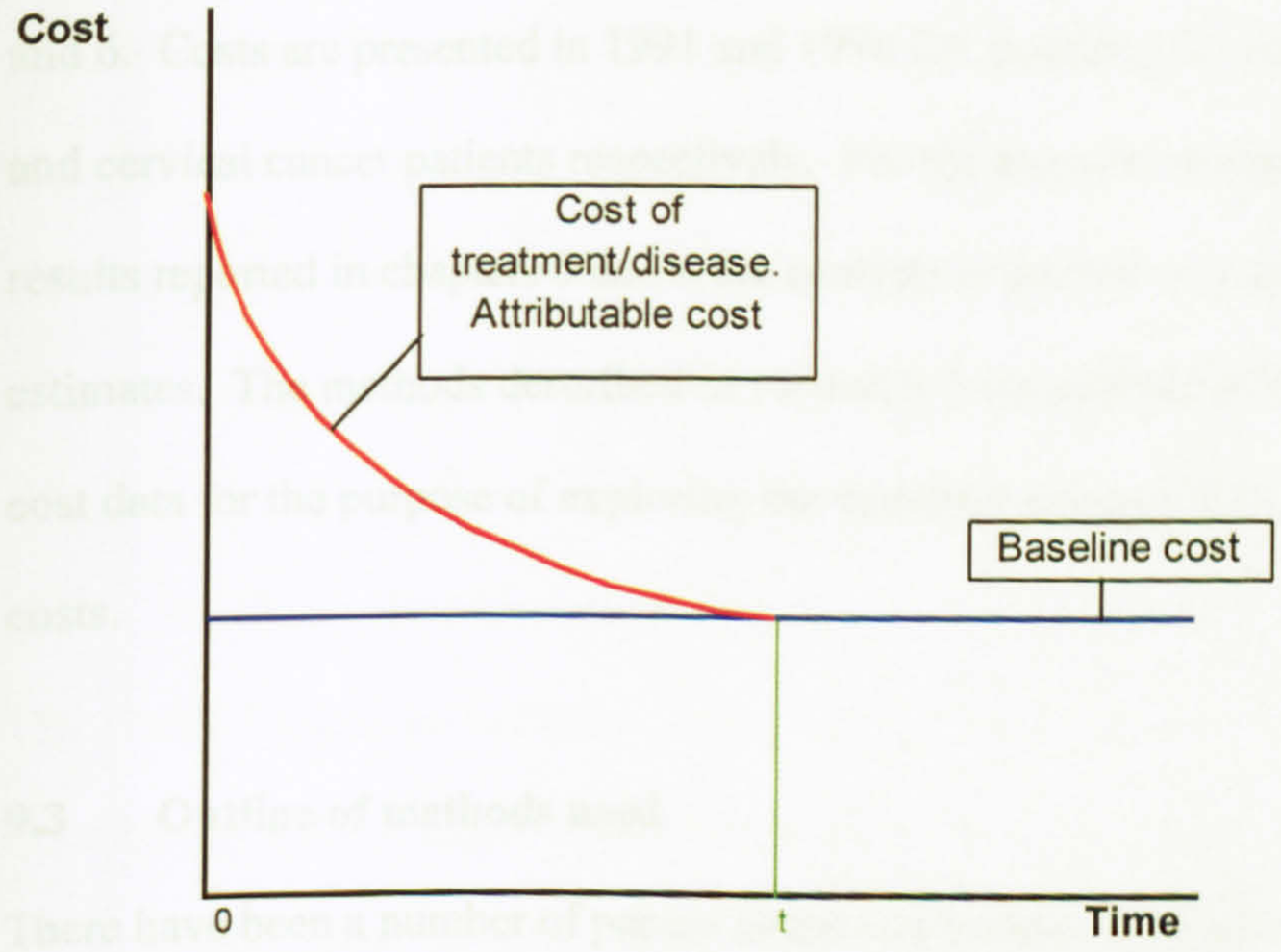
chronic degenerative diseases e.g. Alzheimer's disease, the appropriate time period might be from diagnosis until death, whereas for certain interventions such as hernia repair or appendectomy, shorter follow up periods are required as patients are likely to return to 'normal' or 'baseline cost' within twelve months.

Unfortunately, medical cost data are rarely available for all patients over the whole specified length of follow up. Patients whose follow up is terminated prior to the study endpoint are said to be 'right censored'. All that is known about their survival time (or time to specified event) is that it exceeds the time from diagnosis to last contact. Right censoring can occur in both prospective and retrospective data collection. In prospective studies, for example with the collection of resource use and unit cost data alongside a trial, censoring may arise due to the treatment continuing beyond the end of the trial period or more usually due to patient attrition (drop-out) before the end of the trial period. For retrospective studies patients may be right censored due to the choice of time horizon over which the data are extracted from the medical notes.

Censoring is a particular problem for chronic diseases, where treatment costs are expected to continue over the patient's lifetime. Of course it is plausible to report within trial costs or costs per period of time (as were reported for the breast and cervical data in chapters 5 and 6). However, censoring will inevitably still exist within this defined period so there remains the problem of how to calculate unbiased costs. Although several techniques have been proposed in the published literature since 1995(1-9), studies have continued to estimate mean costs by using the average total costs from all study subjects. This chapter explores the use of techniques to overcome

the bias from censored cost data using the breast and cervical cost datasets analyzed in Chapters 5 and 6.

Figure 9.1 Follow up of patients cost-generating events



9.2 Comparison of methods – an empirical example

In chapters 5 and 6, the average cost of breast and cervical cancer by stage were estimated using the sample mean of observed costs for all study patients over a respective four- and five-year period. However, where data were censored prior to the end of the full four and five years of follow up a monthly value was imputed based on the average monthly cost of the previous twelve months costs for that patient. This method is similar to the 'last value carried forward' method(11).

For breast cancer costs, data were collected on 137 patients diagnosed with breast cancer in 1991. This permitted a resource audit for patients over a minimum period following diagnosis of 46 months and a maximum of 60 months. For cervical

cancer costs, data were collected on 260 patients diagnosed with cervical cancer in 1990. This permitted a resource audit for patients over a minimum period following diagnosis of 59 months and a maximum of 77 months. Resource items included diagnostic, staging, treatment and follow up procedures already outlined in chapters 5 and 6. Costs are presented in 1991 and 1990 UK pounds, discounted at 6% for breast and cervical cancer patients respectively. For the purpose of comparison with the results reported in chapters 5 and 6 the analysis is limited to 4- and 5-year cost estimates. The methods described in section 9.3 are applied to the breast and cervical cost data for the purpose of exploring the variation between the estimated average total costs.

9.3 Outline of methods used

There have been a number of papers proposing various methods to calculate average total costs in medical care. These include:

- Ignoring the issue of censoring altogether (full-sample method),
- Using all available cases (available case analysis)(10),
- Imputation(11)
- Prorating costs(9),
- Discarding cases where data is censored (complete case analysis)(10),
- Standard Kaplan Meier survival analysis techniques (where the variable 'cost' is used in place of the variable 'survival time' by attaching a censoring indicator to observed total cost)(1, 2),
- Use of the Kaplan Meier sample average approach(3, 5-9).

9.3.1 Ignoring the issue of censoring

This method of estimating average total costs completely ignores the issue of censoring (full-sample method; (Average cost = TC month 1 + TC month 2 + TC month 3 +.....TC month t)/number of cases). It effectively treats the censored individuals as if they have died or been discharged from care. The average total cost is therefore estimated using the sample mean of observed costs for all study patients. This method underestimates the true average total cost because any costs incurred after censoring are not accounted for. The degree of bias is dependent on the number of censored subjects in the sample, and is minimal if the number is small.

9.3.2 Available case analysis (ACA)

This method estimates the mean for the complete cases for each variable, then sums the means (total average cost rather than average total cost above). The major disadvantage is that different sample sizes are used across the analysis i.e. the sample base varies from one variable to another. Hence standard parametric statistical inference cannot be addressed.

9.3.3 Imputation

Imputation can be undertaken in a number of ways, two of the most popular forms are "mean imputation" and "last value carried forward". Mean imputation involves the calculation of the mean of the observed data for each variable and the substitution of this value into every case with a missing observation for that variable. However, by imputing the mean value in a number of cases the estimated variance or standard deviation for that variable will be underestimated (since the imputed values do not differ from the mean or each other). The last value carried forward method uses the

last observed value to fill in the missing values. This method only applies to data where repeated measures have been made on the variable in question. The advantages of this method are that it is easy to implement and understand and also allows for complete data methods to be employed. The disadvantage is that it will produce poor results where variables are expected to change over time.

9.3.4 Prorated costs

This method is simple to implement, but assumes a constant cost accumulation over time. The formula is:

(mean cost/ mean follow-up time)*mean survival time

Where mean survival time is based on the Kaplan-Meier survival method.

9.3.5 Complete case analysis

Complete case analysis (CCA) or listwise deletion of cases is the default method in most statistical software packages. It involves discarding all censored cases. The advantages of using this method are that it is easy to do and that the same set of data (albeit a reduced set) is used for all analyses. However, it is inefficient in that it excludes data that are potentially informative for the analysis. Furthermore, CCA will be biased if the uncensored cases systematically differ from the censored cases (e.g. if not missing at random). In practice, CCA is likely to be an acceptable method with small amounts of missing data (say where more than 90% of cases are complete)(10).

9.3.6 Survival analytic techniques

Fenn and colleagues (1995,1996) have proposed the use of survival analytic techniques for the analysis of censored cost data(1, 2). To introduce their method it is necessary to provide a brief summary of the Kaplan-Meier (K-M, also known as the

product limit) method for estimating survival. It is a non-parametric method and therefore requires no assumptions about the distribution of survival times. The only assumption made is that the survival times are independent of the censoring mechanism and that the individual survival times are independent of each other. An example of where this assumption may be violated is where those patients experiencing adverse reactions or poor health compared with the remainder of the sample are more likely to drop-out/ be censored.

The estimator of the survival function is defined as follows:

$$\hat{S}(t) = \prod_{j=1}^{k} \frac{n_j - d_j}{n_j}$$

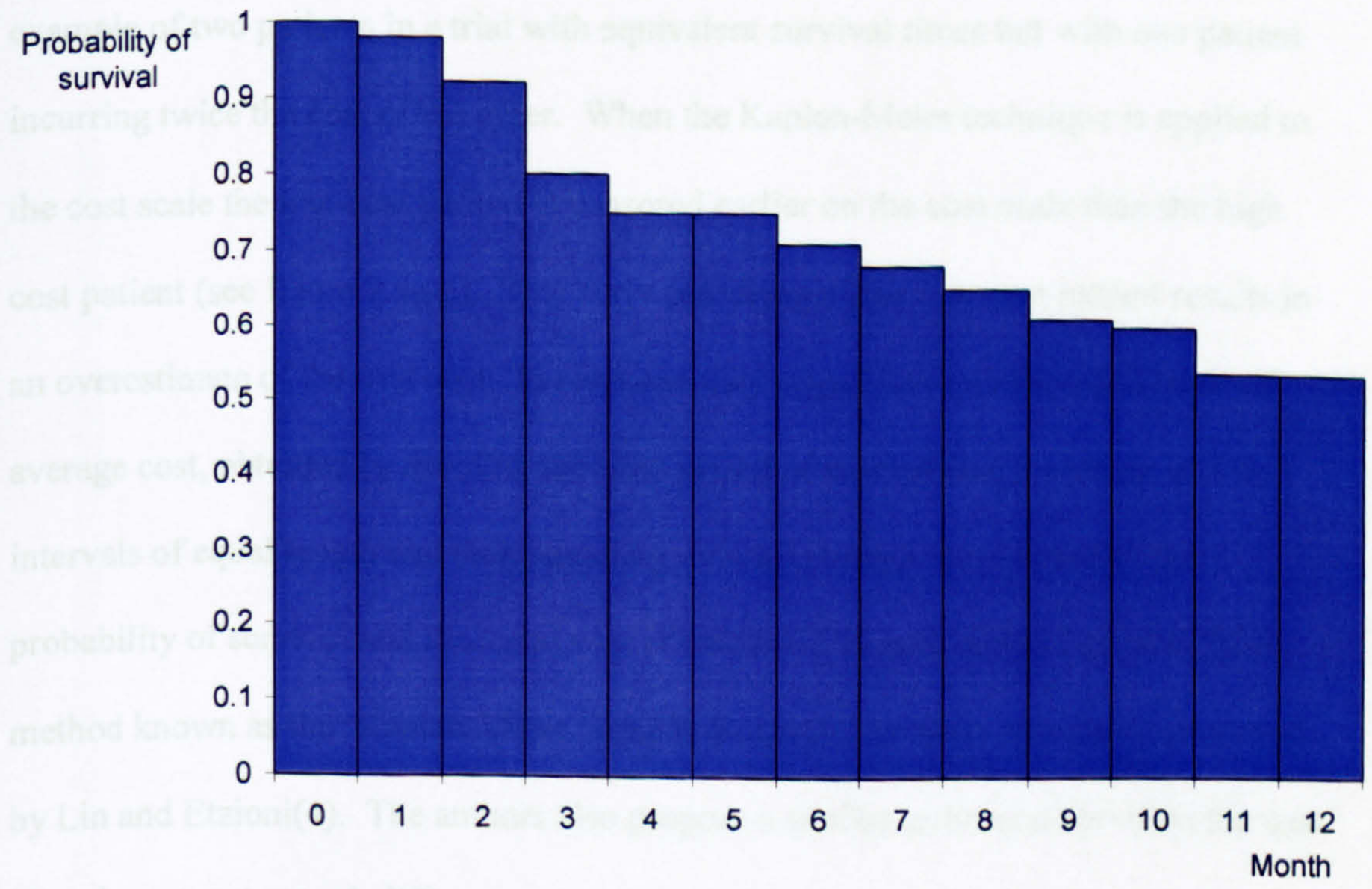
Where n_j denotes the number of people alive at time t_{k-1} and d_j is the number of deaths at time t_k. To illustrate this process, it can be seen in figure 9.2 that patients are followed up for a total time of $t_{kmax} = 12$ months. Everyone is alive at the start of the period and in the first month no one dies or is censored so the probability of surviving for 1 month $P_1 = 1$, At the start of the second month the number of patients at risk is 96 (equivalent to the number at risk at the beginning of the first month minus the number of patients who died or who were censored within the first month), the conditional probability of surviving the second month having survived the first month P_2 = the number of patients followed for at least 1 month and who also survive month 2 (equivalent to the inverse function of the hazard rate (Ht). The Kaplan-Meier survival estimate (St) for the 12-month period is the product of all the conditional survival probabilities up to t_{12} ($Pt_1 * Pt_2 * Pt_3 \ldots Pt_{12}$). A survival plot of the Kaplan-Meier probabilities can then be drawn as a step function (see Figure 9.3). It is possible to

determine the mean and median survival time by estimating the area under the curve (steps) and the point at which 50% of the study population are still alive, respectively.

Figure 9.2 Kaplan-Meier example

Time period	No. at risk	Deaths	Censored	Ht	Pt	St
0	100	0	0	0	1	1.00
1	100	2	2	0.02	0.98	0.98
2	no at risk in t1-(no of deaths and censored in t1)	6	8	No of deaths in t2/no at risk at start of t2	1/hazard (Ht)	Pt1*Pt2
3	82	11	3	0.13414634	0.865854	0.80
4	68	4	1	0.05882353	0.941176	0.75
5	63	0	0	0	1	0.75
6	63	3	2	0.04761905	0.952381	0.71
7	58	3	1	0.05172414	0.948276	0.68
8	54	2	6	0.03703704	0.962963	0.65
9	46	3	3	0.06521739	0.934783	0.61
10	40	1	5	0.025	0.975	0.6
11	34	3	1	0.08823529	0.911765	0.54
12	30	0	30	0	1	0.54

Figure 9.3 Kaplan-Meier survival plot



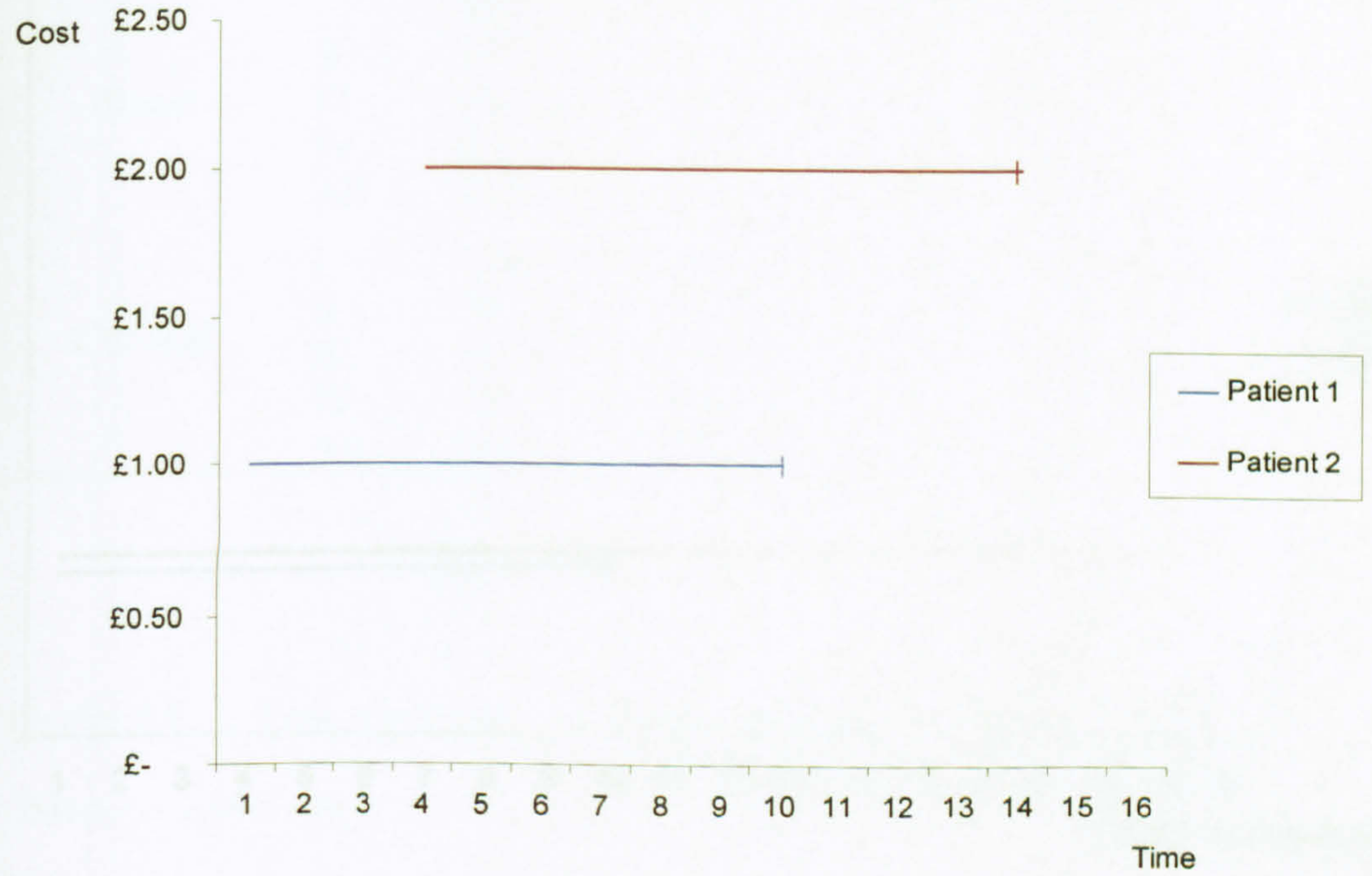
Fenn and colleagues apply this Kaplan-Meier technique employing cost as the metric in place of time. The average total cost is estimated by calculating the area under the curve. This method had previously been used by two separate US research teams; Adams-Dudley and colleagues and Rutten van Molken and colleagues for use in cost prediction(11, 12). Fenn and colleagues also used alternative parametric survival analysis approaches such as Cox regression and Weibull functional forms to estimate average costs. However, the K-M method has the advantage in that it is a nonparametric method. Parametric techniques have recognized limitations due to the likely skew of cost data, and presence of a number of observations with zero costs. The use of the Kaplan-Meier technique when applied to the cost scale was later criticized in a paper by Hallstrom and Sullivan, who argued that this method could not be used as the assumption of independent censoring was violated(5). They use an example of two patients in a trial with equivalent survival times but with one patient incurring twice the cost of the other. When the Kaplan-Meier technique is applied to the cost scale the low-cost patient is censored earlier on the cost scale than the high cost patient (see figure 9.4a-c). This early censoring of the low cost patient results in an overestimate of the true cost. In response they suggest an unbiased estimator of average cost, obtained by dividing the time period of interest into a number of small intervals of equal length and then summing over all periods the product of the probability of survival and the mean cost of treatment in each defined period. This method known as the 'Kaplan-Meier Sample Average' has been previously proposed by Lin and Etzioni(4). The authors also propose a similar technique for when the cost histories are not recorded(3).

When cost history available: $\Sigma P(s) * E(c|s)$, where P(s) is based on the K-M and E(c|s) is the average cost during the interval conditional on being alive at the start of the interval. In other words, the mean cost at a given time period t given the probability of being alive at the start of time t is estimated using the cost data from subjects who survive to the start of the time interval t. The estimate is based on the subject costs during the time period t, this includes the cost of cases who survive to the start of time t, but who may die, be discharged or censored during the time period t. Therefore the costs related to death and discharge are included in the average cost estimates for each time period.

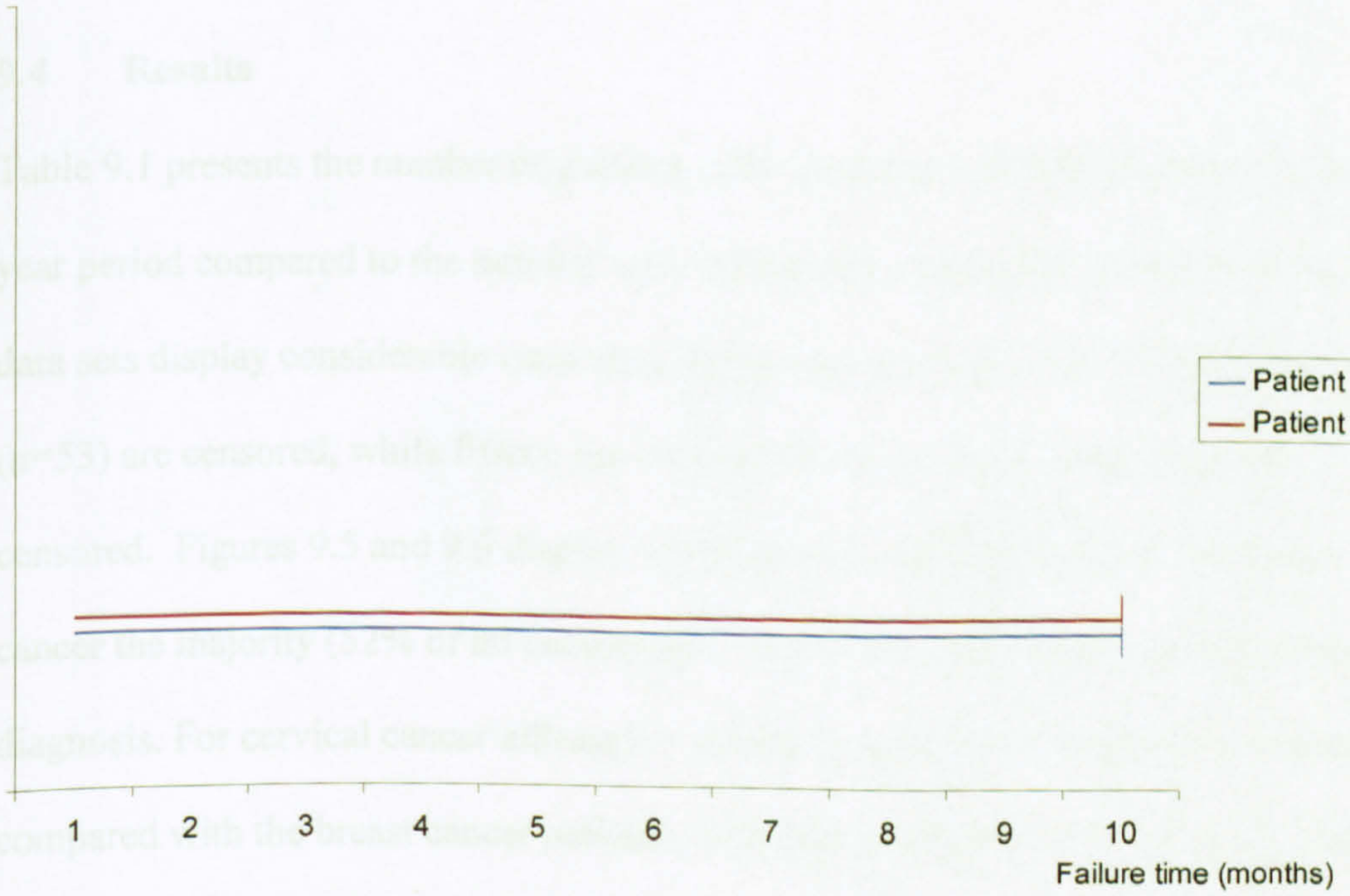
These technical reports were later published as a technical paper(7) and an application paper using the techniques to estimate the average cost of ovarian cancer(6).

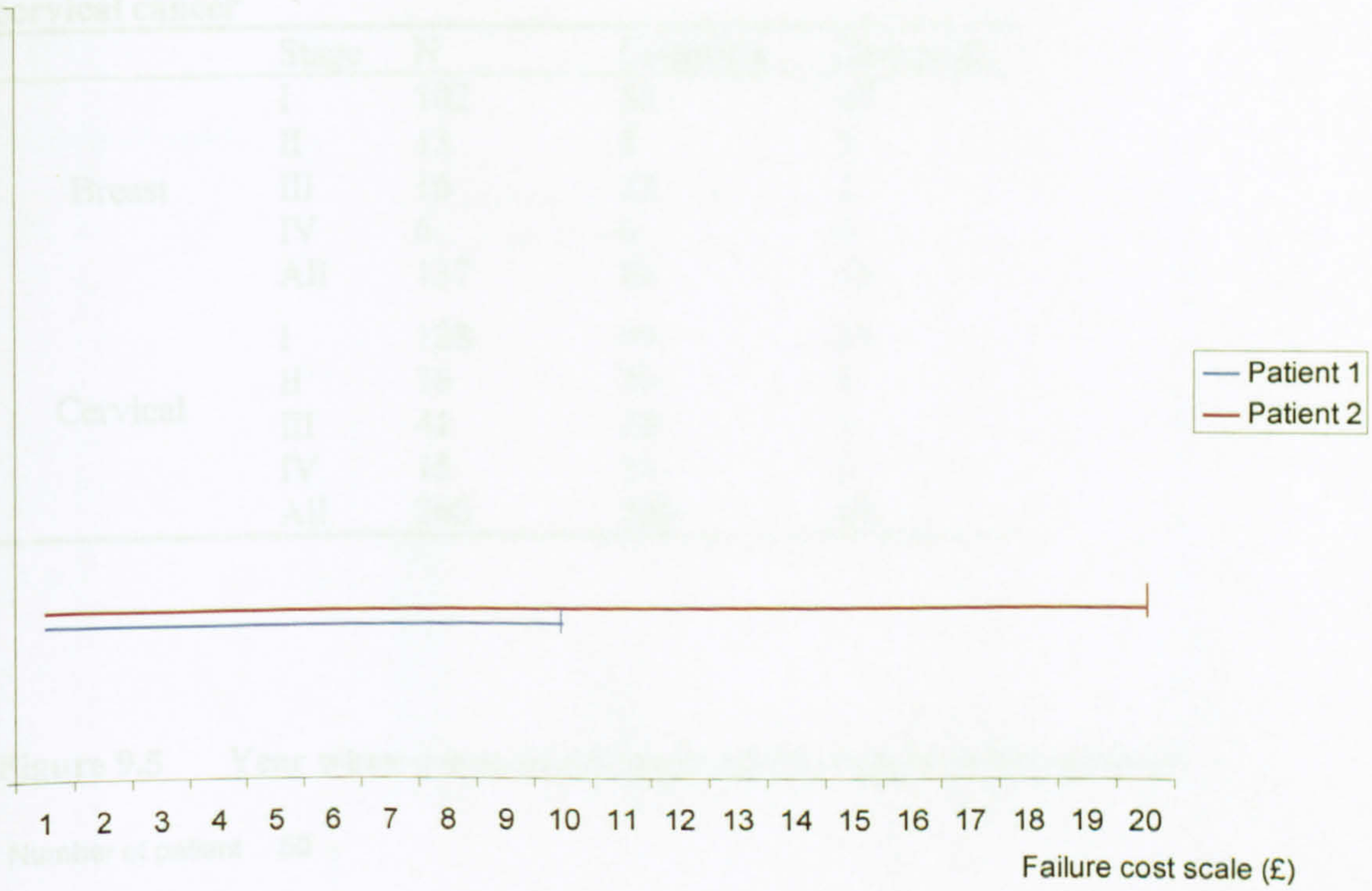
Figure 9.4 Transfer of real time costs to failure time scale and failure cost scale

A Real time costs for patients 1 and 2



B Failure time scale (months)





9.4 Results

Table 9.1 presents the number of patients with complete cost histories over the four-year period compared to the number with incomplete/censored cost information. Both data sets display considerable censoring, thirty-nine per cent of the breast cancer data (n=53) are censored, while fifteen per cent (n=40) of the cervical patients are censored. Figures 9.5 and 9.6 display when the censoring is incurred. For breast cancer the majority (52% of all censoring) is incurred in the fourth year following diagnosis. For cervical cancer although a smaller proportion of patients are censored compared with the breast cancer patients, similarly the majority (45%) of all censoring is incurred in the final year (the fifth year following diagnosis).

Table 9.1 Number of censored and complete cost histories for breast and cervical cancer

	Stage	N	Complete	Censored
Breast	I	102	55	47
	II	13	8	5
	III	16	15	1
	IV	6	6	0
	All	137	84	53
Cervical	I	128	99	29
	II	76	70	6
	III	41	36	5
	IV	15	15	0
	All	260	220	40

Figure 9.5 Year when censoring is incurred for breast cancer patients

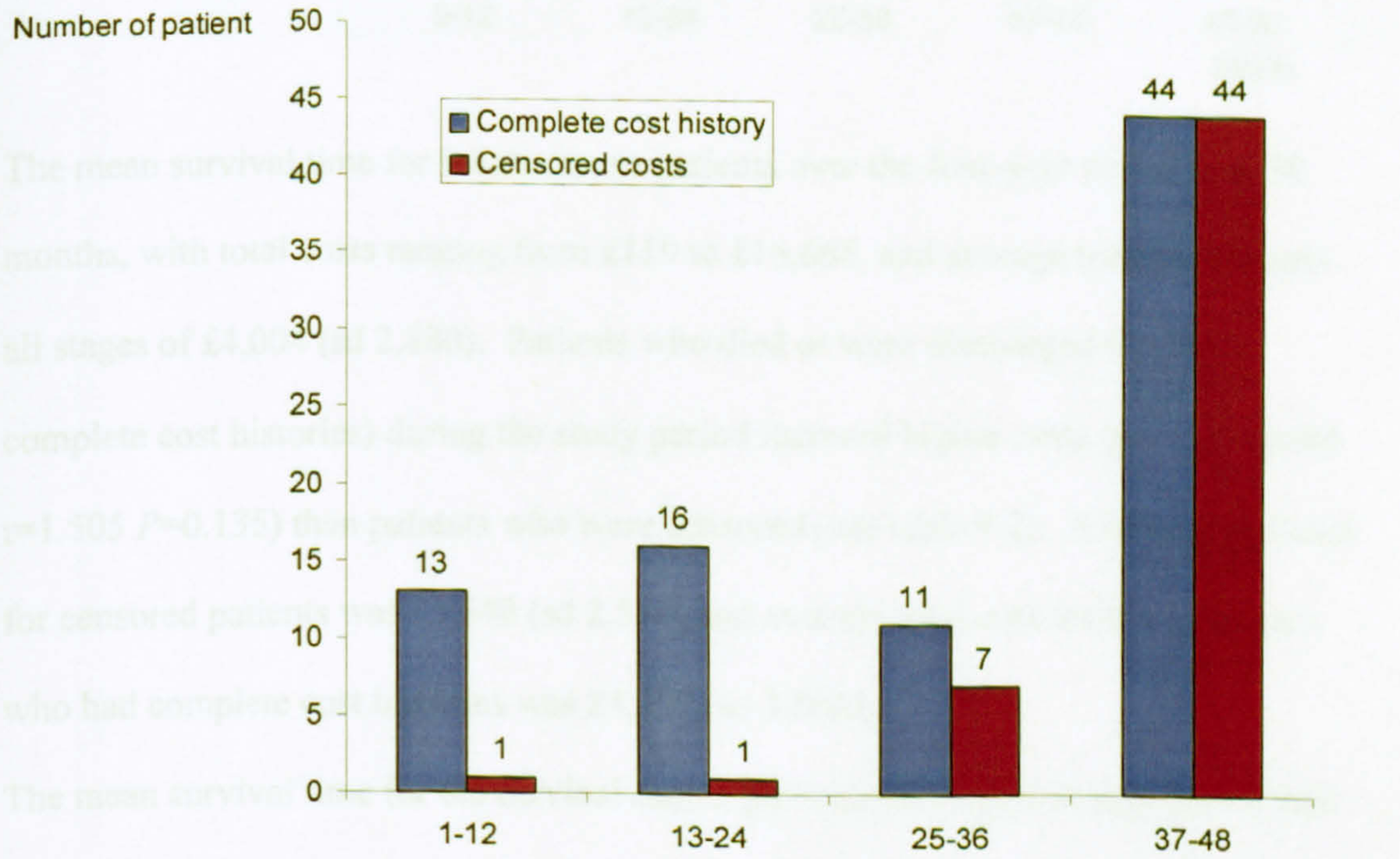
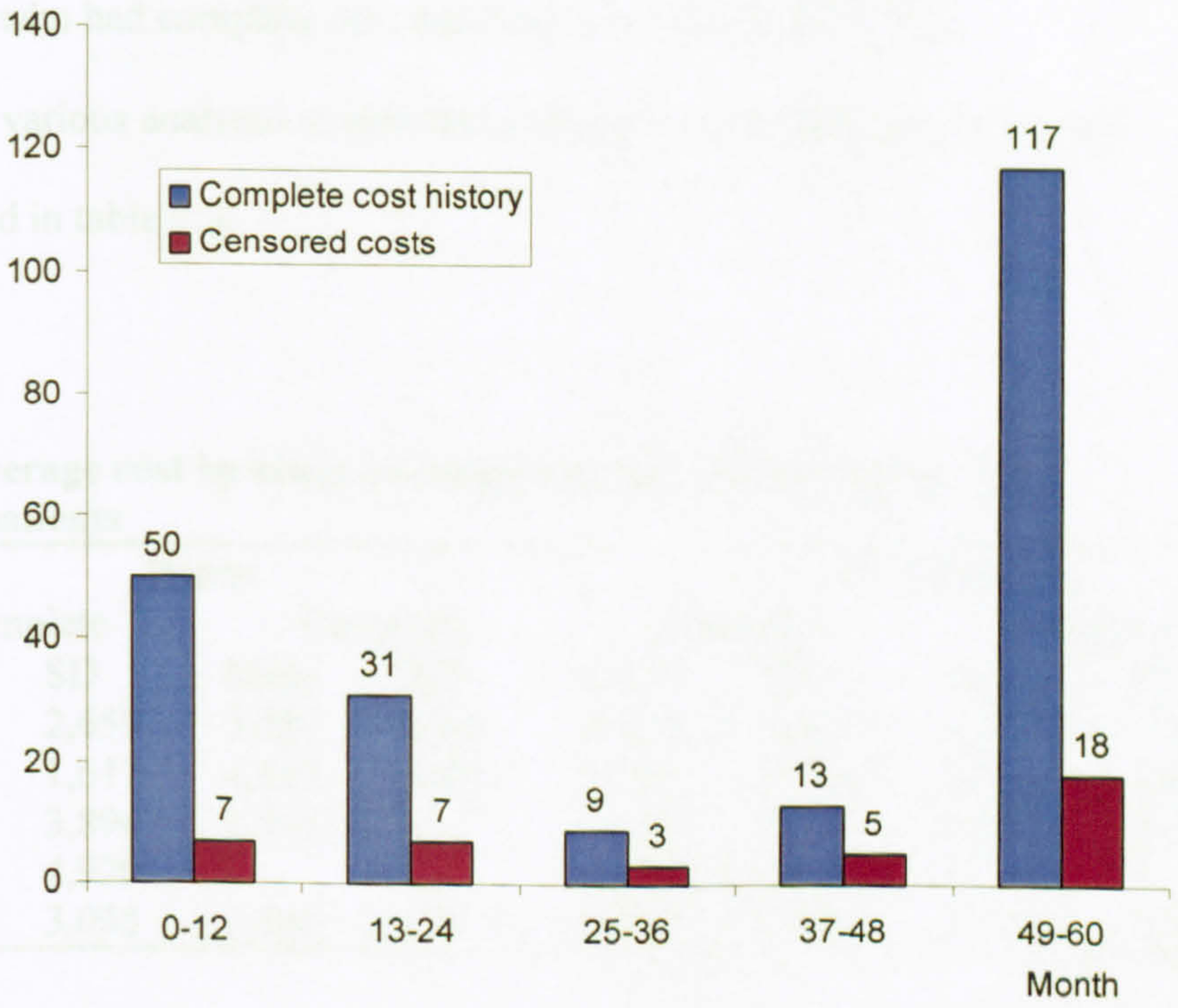


Figure 9.6 Year when censoring is incurred for cervical cancer patients



The mean survival time for breast cancer patients over the four-year period was 38 months, with total costs ranging from £119 to £16,668, and average total cost across all stages of £4,004 (sd 2,880). Patients who died or were discharged (i.e. had complete cost histories) during the study period incurred higher costs (not significant t=1.505 *P*=0.135) than patients who were censored (see table 9.2). Average total cost for censored patients was £3,540 (sd 2,517) and average total cost for those patients who had complete cost histories was £4,297 (sd 3,065).

The mean survival time for the cervical cancer patients over the five-year period was 42 months, with total costs ranging from £48 to £62,523, and average total cost across all stages of £8,749 (sd 7,404). Patients who had complete cost histories including those who died or were discharged during the study period incurred significantly higher costs (t=3.023 *P*=0.003) than patients who were censored (see table 9.2).

Average total cost for censored patients was £5,542 (sd 3,289) and average total cost for those patients who had complete cost histories was £9,332 (sd 7,791).

The results of the various analyses to estimate average costs of breast and cervical cancer are reported in table 9.3.

Table 9.2 Average cost by stage for complete and censored breast and cervical cancer patients

Stage	Breast				Cervical			
	Complete		Censored		Complete		Censored	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I	3,910	2,659	3,487	2,511	6,920	4,993	5,267	3,382
II	4,088	1,617	4,351	2,892	11,122	9,381	6,952	2,421
III	4,900	3,894	1,945	-	11,571	7,175	5,453	3,814
IV	6,613	4,920	-	-	11,535	11,724	-	-
All	4,297	3,065	3,540	2,517	9,332	7,791	5,543	3,289

Table 9.3 Average cost of breast and cervical cancer by method of estimation

Method	Stage	Breast		Cervical	
		Mean	95% CI	Mean	95% CI
Impute costs	I	3,734	3,248-4,217	6,623	5,789-7,452
	II	4,394	2,946-5,841	10,910	8,837-12,985
	III	4,331	2,481-6,179	10,838	8,590-13,085
	IV	6,613	1,450-11,776	11,535	5,042-18,027
Full sample	I	3,715	3,207-4,224	6,546	5,721-7,371
	II	4,189	2,932-5,447	10,793	8,716-12,870
	III	4,715	2,672-6,758	10,826	8,580-13,071
	IV	6,613	1,450-11,776	11,535	5,042-18,027
ACA	I	4,055	-	6,945	-
	II	4,470	-	12,318	-
	III	6,314	-	15,027	-
	IV	11,009	-	15,952	-
Prorated	I	4,040	-	7,165	-
	II	4,577	-	11,094	-
	III	4,860	-	11,978	-
	IV	6,613	-	11,535	-
CCA	I	3,910	3,191-4,629	6,920	5,924-7,916
	II	4,088	2,737-5,440	11,122	8,885-13,359
	III	4,900	2,743-7,056	11,571	9,144-13,999
	IV	6,613	1,450-11,776	11,535	5,042-18,027
K-M	I	5,438	4,461-6,415	7,807	6,696-8,917
	II	4,964	3,623-6,304	11,451	9,216-13,686
	III	4,991	3,035-6,946	11,917	9,602-14,233
	IV	6,613	2,676-10,550	11,535	5,588-17,450
KMSA	I	3,877	-	6,716	-
	II	4,244	-	10,822	-
	III	4,801	-	11,482	-
	IV	6,613	-	11,535	-

9.5 Discussion

The empirical example (table 9.3) using breast and cervical cancer cost data illustrates the variation in average cost estimates obtained by using different methods to calculate the average total medical costs. It has been argued that the full sample method results in average cost estimates that are biased downwards, as they take no account of costs following censoring(1, 2, 7). This argument appears to be borne out by the empirical results in table 9.3.

Attempts to overcome this bias include using other naïve methods such as available case analysis (ACA), complete case analysis (CCA) and prorated costs. All three methods result in higher cost estimates than the full sample method. ACA is not an ideal method for cost estimation for the purpose of economic evaluation as no measures of variance can be obtained from such an analysis. Cost estimates using CCA are inevitably biased towards the costs for patients with complete cost histories. In this example they reflect the costs of those patients who are discharged early, have full cost histories over the four- or five-year period or die from the disease. It is also an inefficient method as the estimates are based on 61% and 84% of the total sample of breast and cervical patients respectively. The prorated method is likely to be a biased estimate as the basic assumption for using this method is a constant accumulation of cost over time. This is not the case with either the breast or cervical cancer costs (see figures 9.4 and 9.5).

Use of the K-M method using costs in place of time as the metric for the survival analysis results in extreme overestimation of average costs. This overestimation has also been found in previous studies using this method proposed by

Fenn and colleagues(1, 2, 7, 8), and is due to the early censoring of the low cost patients.

The final method employs the Kaplan-Meier sample average to produce an unbiased estimator of average costs. This method allows for censoring by weighting the costs using the K-M survival estimates. For breast and cervical cancer, these cost estimates are higher than the full sample estimate and lower than the estimates produced by the CCA, prorated and K-M methods (except for stage IV cancer costs where cost histories are complete for all patients). Figures 9.4 and 9.5 display the cumulative cost functions for the KMSA method compared with the original cost data, it can be seen how the KMSA takes account of any censoring during each period, resulting in slightly higher costs than those for the full sample method. Of course if 95% confidence intervals were to be calculated for the estimates produced by the different methods, it would appear from table 9.3 and figures 9.4 and 9.5 that variation in results produced by the alternative methods would probably not significantly differ from one another.

There are drawbacks to using the KMSA method, in that it is recognized that smaller time intervals produce more efficient cost estimates. This requires resource use data to be collected, stored and analyzed in the database on a monthly interval basis. Compared with collecting, storing and analyzing data in an annual format this is a more time-consuming process.

Another issue related to the length of the interval is the assumption that has to be made by the analyst as to whether censoring occurs at the start or end of the interval. In this example I have made the assumption that all censoring is incurred at

the end of the interval (see table 9.4), so that at the start of the analysis everyone is assumed to be alive thus the probability of survival S(t1) in the first month is 1. For stage III breast cancer patients this survival probability drops to 0.878 in the second month. If I was to assume that all censoring was incurred at the start of the period the average cost estimates would be lower than those reported in table 9.3. For example for stage I breast cancer costs the assumption of censoring at the start of the interval results in an average cost estimate of £3,858 compared with £3,877 when censoring is assumed to be incurred at the end of the period. Lin et al, (1997) point out that this assumption is the worst scenario as the censored patient has a zero observed cost in the censoring interval(7). They also mention that the amount of bias for this estimator depends on the amount and timing of censoring and diminishes as the intervals shrink. They suggest that monthly intervals are more than adequate. Intervals of an annual basis may be problematic, as cases censored during the year may significantly under-contribute to the sample mean cost for that year.

As this is a relatively under-researched area, there are few studies available for comparative purposes. Using work reported by Lin and colleagues, it would seem that these results are consistent with what is expected. Lack of significant differences in cost estimates may be a result of smaller sample sizes being used in this analysis.

It would appear from the results in table 9.3 that none of the techniques used actually change the conclusions made in chapters 5 and 6 concerning the cost-by-stage differences for breast and cervical cancer. Therefore use of the rather naïve imputation method employed in chapters 5 and 6 appears to be a plausible method to apply. However, it is currently impossible to tell whether similar conclusions would

be reached for the analysis of censored cost data with respect to other diseases, or with the advantage of using larger datasets. It is apparent that the Kaplan-Meier method using cost rather than survival and the available case analysis

9.6 Conclusions

Unfortunately from the results reported in this chapter, and the limited empirical publications on the use of analytic methods for censored cost data, it is impossible to make any firm conclusions. The presence of censoring does present real methodological and practical problems for the estimation of mean total costs. However it is too early to tell whether, the methods proposed do actually make a difference to the results, moreover, it is currently unclear how to best judge between the techniques. The results obtained in this chapter are limited to a specific disease, it may well be that one would get different results from the analysis of censored cost data for different diseases or interventions.

One important conclusion that can be drawn from this chapter is that, when undertaking any analysis of cost data, information on the number and proportion of patients with complete and censored costs should be routinely reported along with the method used to take account of the censoring.

Table 7.4 Assumption of censoring at end of period

Month	KM survival	AC	KMSA
1	1	5917.72	5917.73
2	0.878	2274.63	1997.13
3	0.8028	426.57	342.45
4	0.7777	401.05	311.90
5	0.7526	187.06	140.79

Figure 9.7 Comparative cumulative breast cancer costs over the 4-year period with full sample method, available case analysis and KMSA.

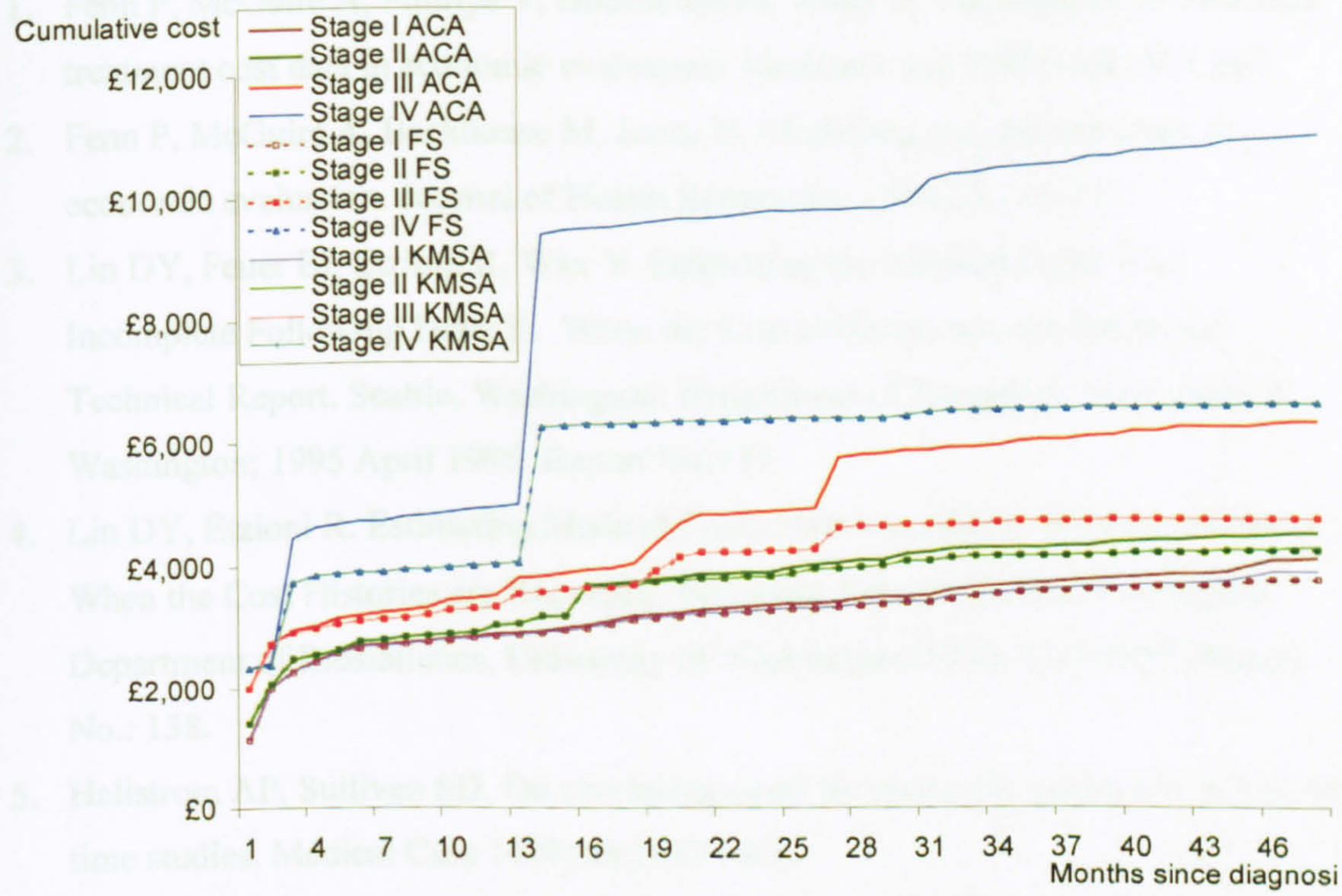
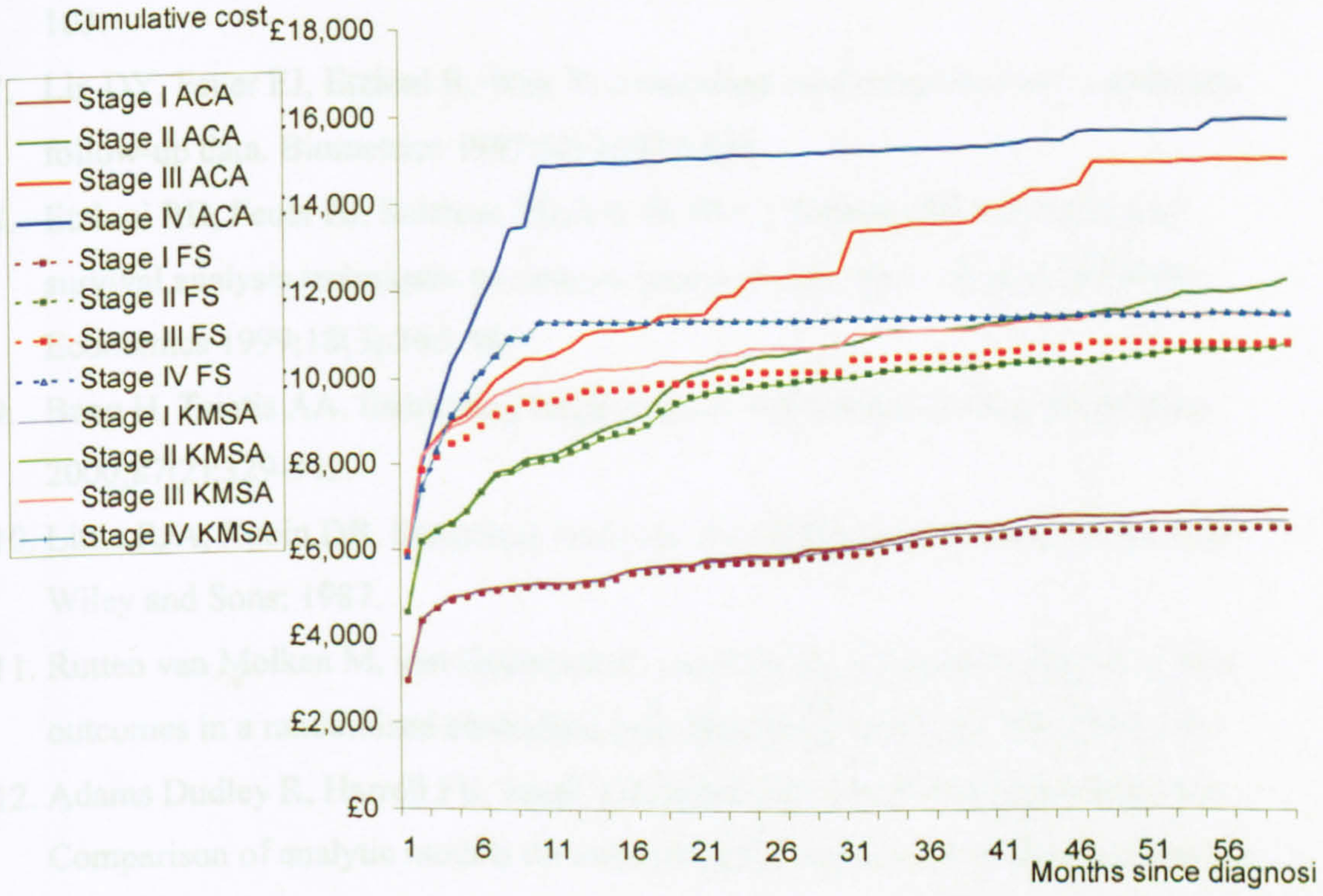


Figure 9.8 Comparative cumulative cervical cancer costs over the 5-year period with full sample method, available case analysis and KMSA.



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Chapter 10

Discussion

10.1 Introduction

This chapter discusses the empirical findings of this thesis in relation to three important areas.

The first topic for discussion is how the experience of costing in practice complies with the principles of costing set out in chapter 2. The literature review in chapter 3 has already alluded to the problems of costing in practice, and highlighted the divergence from how costs ought to be estimated in order to conform to economic principles. Section 10.2 explores the problems encountered when trying to adhere to the theory and guidelines, with reference to the empirical chapters 5-9. In particular it explores the issues of choice of perspective and the reality of using average costs in place of 'true' opportunity costs or even marginal costs.

Throughout this thesis an acknowledgment has been made of the considerable length of time required to collect the data and undertake such a costing exercise. Therefore the second subject for debate is whether the results could have been achieved using a less-time consuming method of estimation. For example, would length of stay have been a good enough predictor of costs

compared with those estimated by abstracting detailed information on all cost-generating events from patients' medical notes.

The final area of discussion is centred on the policy implications of the results reported in chapters 5-7. The focus for this part of the discussion is on the potential users/audience of these results and how the findings might be used.

10.2 Theory and practice of costing

Chapter 2 outlined the principles of costing for the purpose of conducting an economic evaluation. However when actually conducting a costing exercise, as was undertaken for breast, cervical and lung cancers in chapters 5-7, it appears that there are two main divergences from the economic theory that underpins the principles of costing. Namely, the application of the societal perspective and the use of opportunity costs.

The majority of existing economic evaluation guidelines argue that a societal perspective should be used for all analyses(1-4). The societal approach has been recommended as the standard perspective for costing, as it allows the analysis to be carried out on a number of viewpoints. In practice the societal perspective may be neither attainable nor of interest for the users of the results. For example, in costing the cancers for this thesis, a hospital-based perspective was taken. The reason for this choice of perspective is that Trent health authority, in defining what they wanted to know (i.e., the resources and costs used by the regions' hospitals in diagnosing and treating cancer), set the perspective. If the purpose of the costing exercise had been specifically for an economic evaluation

of an anti-cancer drug aimed at palliation in end-stage disease, the omission of other costs, such as informal care costs, could have been problematic. The drug may have had the effect of reducing the burden on informal carers, and if this cost had not been included the important effect would not have been quantified in the results. Therefore the choice of perspective and hence the costs to be estimated are dependent on the context and the question being asked. It should not be the case that all studies take the societal perspective, although, awareness of all the possible costs is important.

The second issue of contention encountered while conducting the costing for this thesis was the use of average costs in place of opportunity costs. According to economic theory, the true cost in any economic analysis is the opportunity cost. It is measured as the benefits that would result from the next best alternative use of the foregone resources. Opportunity cost is difficult, perhaps impractical, to estimate precisely. In practice market prices are generally used and accepted as approximations to opportunity costs. Average costs rather than opportunity costs were used in this thesis. The choice in this case was felt to be justifiable on two counts. Firstly, it was felt that the use of average cost estimates were appropriate for the question being asked, 'what is the current cost to our region of providing cancer'? Secondly, it was felt that any attempt at obtaining 'true' opportunity costs or even marginal costs for all three cancer sites would require a significant amount of research time. From the experience of costing in practice I feel that obtaining 'true' opportunity costs may in reality be impossible for any disease or intervention given the time and financial constraints.

Costing the cancers in this thesis required resource use information across a number of specialities (even, as in this case, when confined to estimating the hospital costs). Cancer treatment entails such specialities as surgery, chemotherapy, radiotherapy, diagnostic imaging, inpatient stays for complications to name a few. Invariably these interventions were conducted at different centres within the hospital or at different hospitals, with each department holding their own medical notes on the exact details of the treatment. For example the radiotherapy departments detail all the treatment planning and number of fractions of radiotherapy undertaken on a certain patient while the chemotherapy departments detail the drugs and doses used. Given the complexities of cancer care, obtaining accurate information on all the resources used for the care of breast, cervical and lung cancer patients and then placing a value that reflects the 'true' opportunity cost on these resources would not be possible in practice. One would have to measure and value all the resources used in terms of foregone benefits. This would be conducted by asking an expert (clinical director, clinician, ward manager) to identify the marginal patient to be admitted to a ward or radiotherapy unit and suggest the benefits arising from not admitting this marginal patient, then one would have to place a value on these benefits that could be incorporated into an economic analysis. These estimates of 'true' opportunity costs are unlikely. Even if the expert was able to identify the benefits arising from freeing up the resources from the marginal patient on the ward, trying to value this benefit in units that can be used in an economic evaluation is a complex task, and even if undertaken may still not reflect the true opportunity cost. The alternative

to 'true' opportunity costing is the use of marginal costs. However, this is still reliant on obtaining (often subjective) information on the resource implications from not admitting the marginal patient, which include number of hours and minutes of staff time, consumables etc. and then valuing the resources at market prices. In this thesis conducting this task for all resource events (all diagnostic, surgical, radio-therapeutic, cytotoxic etc.) would have been impractical, hence the use of average costs. Given the practical side of costing in this thesis, I would suggest a more useful way of presenting cost information is to provide separate information on resources used and released and then to attempt a valuation of them using market prices. Then even if the decision maker does not agree with the valuation aspect, s/he does have information on the basic resource use.

10.3 Is it possible to reduce the research time required without jeopardising the findings?

One criticism that can be levied against the costing method used for the purpose of this thesis is its time-consuming nature (even without estimating true opportunity costs). There are two possible alternatives available to reduce the amount of research time required. First, use of a smaller sample of patients, or a sample limited to one hospital. Second, use of length of stay as a proxy for total cost.

The problems associated with using a smaller sample of patients for the cost estimation can be discussed using the breast cancer sample as a particular example. Only 82 per cent of the initial sample of 200 patients met with the inclusion criteria or could be traced, and of these only 137 were used to produce

meaningful cost estimates by stage of disease. It is not surprising to find that, because end stage disease is rarer than stage I cancer and because it was impossible to stratify and sample according to stage prior to obtaining the information from the medical notes, the number of stage IV cancers in the sample amounted to only 6 patients. Fortunately, the costs of these cancers were found to be significantly higher than the other disease stage costs despite the small sample size. Having an even smaller sample size might have jeopardized this finding. In fact one may question whether the results may have changed if a larger sample size had been used.

An alternative to reducing the actual sample size is to reduce the number of centres/hospitals from which the resource use information was collected. It might be argued that collecting the data from a single hospital should be sufficient. However, this would have reduced the variability of the results. The cervical cancer cost data ranges from £6,300 in Barnsley to £11,700 in Bassetlaw yet do not vary significantly between the 12 districts ($F = 1.277$, $P = 0.237$). The use of different hospitals in different districts in the Trent area also meant that the results are likely to be generalisable to other areas in England and Wales, as the region has a mix of urban and rural areas, ethnicity and teaching and non-teaching hospitals.

The second possibility for conducting the research at lower cost is to use length of stay as a proxy for total care cost. Previous studies have shown that inpatient length of stay is a good predictor for total cost of care(5, 6), therefore the product of average length of stay and the unit cost for an inpatient bed day could

be used as a proxy for total care costs. However, there are a number problems involved in estimating such a proxy and limitations associated with its use.

In order to estimate the proxy measure of cost, information on inpatient length of stay is required. Routinely collected statistics on inpatient admissions and length of stay for patients in England and Wales can be obtained from the Hospital Episode Statistics (HES)(7). This information is made available to the Office for National Statistics (ONS) by individual hospitals from their computerised patient administration systems (PAS). The data are limited in that the ONS only uses a 25% random sample of all inpatient episodes to inform the HES, neither patients nor hospitals are identified and individual episodes are not linked. Moreover the ONS acknowledge problems with the completeness of the PAS in recording resource events. The HES provide information on the number of inpatient days and mean length of stay in Trent for breast, lung and cervical cancer by ICD code. For England and Wales data are also provided on the number of inpatient episodes by type of procedure, although these categories are rather generalised, for example for breast cancer, the procedures are, 'excision of the whole breast', 'other excision' and 'biopsy'.

By combining the 3, 5 and 10 days length of stay for Trent breast, cervical and lung cancers as reported by the HES with the unit cost estimates for an inpatient day used in chapters 5-7, the estimated average cost for breast, cervical and lung cancer amount to £542, £1,083 and £1,861 respectively. These average care costs are significantly lower than the results using the detailed costing methods. Moreover, use of inpatient length of stay information from the HES

would not enable an analysis of the costs by stage of disease or by other socio-demographic factors. Nor would the proxy measures allow for any statistical analysis of the cost data to provide information on the variability of the results, only a point estimate would be provided. The use of length of stay data would also limit any analysis of where the cost burden falls within the total care package. For example, with the breast cancer data a large proportion of the diagnostic and radio-therapeutic events were undertaken on an outpatient basis, and using any data on length of stay would mean these events would be excluded from the cost calculation.

An alternative database to the HES exists for inpatient episodes in Scotland. These are the linked 'Scottish Morbidity Records' (SMR). It is unique to the UK and suited to the work conducted in this thesis. It documents all hospital admissions from 1981, it is also possible to identify individual patients and hospitals, it covers the whole of the Scottish population and all episodes of care for the individual are linked.

10.4 Policy implications and potential users of the findings from this thesis

There are a number of potential users of the findings from the work conducted in this thesis. They include key decision makers such as health authorities, hospital trusts and the National Institute for Clinical Excellence (NICE) and are also likely to be employed by other researchers.

Trent health authority used the findings to determine their current level of spending on specific cancers. Health authorities surprisingly have limited

knowledge of their current spending on specific disease areas, let alone the costs of specified treatment options within a disease area. The work conducted for this thesis therefore has not only provided information on the overall cost of breast, cervical and lung cancer in Trent, but has also highlighted the resource use and costs related to the diagnostic, therapeutic and maintenance events that in combination make up the total hospital care costs. Given the data were collected from various districts within the region and from patients with differing socio-demographic backgrounds, the results are felt to be generalisable to other regions in England and Wales.

Another possible use for these results is in the commissioning of care for the region. At present, cancer services are commissioned by health authorities using a process of health needs assessment and the setting of service agreements (contracting). The health authority and trusts negotiate these service agreements based on finances and the number of outpatient, day case attendances and finished consultant episodes (FCEs). These are negotiated separately with different trusts, and acute and community service agreements are totally independent. With cancer services another problem is that the pharmacy budget is also negotiated separately. There are therefore a number of problems with the current process. It is fragmented; the process of commissioning cancer services with different trusts results in a discontinuity of care. It is inflexible; because the budgets are decided for each sector, (acute, community, pharmacy) separately, any savings generated in one budget cannot be used for another budget. It creates perverse incentives; there is no incentive for clinicians to make cost-effective changes to the way they

deliver their care, as it is likely that any savings made would be used for another speciality rather than to treat the same condition. There is therefore a need to change this current process of commissioning care. An alternative is to commission according to a care protocol or pathway, as developed in this thesis. The care pathways, with numbers of patients and resources used for each stage of the pathway could determine the cost of each stage, which in turn could inform the contract. By using the type of care pathways, resource use and costs developed in this thesis, commissioning could be undertaken on a 'whole systems approach' that would eradicate the problems inflexibility and perverse incentives associated with the current method. The care pathways would be modified and monitored under clinical governance arrangements as part of audit, and would provide health authorities with information on the resources spent each year on specified disease areas or treatments. The only clear barrier to change is the present lack of linked databases on episodes of individual patient care. If England and Wales could adopt the system of the linked Scottish morbidity records, then commissioning according to the care pathways developed in this thesis would be feasible.

The National Institute for Clinical Excellence (NICE) is another key decision-maker that could use the cost results reported in this thesis to determine the impact of their decisions on the total cost of breast, cervical and lung cancer. In summer 2001 they are due to announce whether specific anti-cancer drugs should be made available to cancer patients. For those drugs used to treat lung and breast cancer NICE could use the cost results reported here to inform health

authorities on how much the cost of implementing these drugs is likely to be as a proportion of their current total spending on those cancer sites.

Other researchers are also potential users of the cost results. For example, the estimation of cervical cancer costs is extremely pertinent to the current research into HPV testing. Before such a programme can be introduced, the National Health Service requires evidence of its effectiveness and cost-effectiveness. Therefore there is potential for these UK based cervical cancer cost estimates by disease stage to be employed in such an analysis. Similarly the breast cancer cost results could be used to assess the impact of changes to the UK breast screening programme such as amendments to the screening interval or the age range. And the results from the lung cancer costing exercise could be used to assess the impact of any programme likely to reduce the numbers of lung cancers in the UK, such as smoking cessation or radon remediation(8).

The key to the use of the cost data for all the above purposes is that it is UK based. No other detailed cost study of breast, cervical and lung cancer has been undertaken in the UK. Moreover, the method used for costing these cancers allows for a distinction to be made between disease characteristics or the socio-demographic background of the patients.

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Chapter 11

Conclusions

11.1 Introduction

The purpose of this thesis was to explore the theory, practice and application of costing with specific reference to cancer. In part it has reviewed the theory and guidelines related to costing methods including the recent focus on the analytical techniques used with cost data. In addition it has examined how these theories and guidelines are applied in practice, by reviewing the literature on costs and cancer. The empirical research in this thesis applied costing methods to three specific cancer sites; breast, cervix and lung. This analysis provided information on the total burden of these specified cancers in terms of cost to a typical health authority (Trent). It also explored the hypothesis highlighted in previous studies that the cost of cancer increases with the stage of the disease. The final area of contribution for the thesis is in the application of recently suggested analytical techniques for cost data to the breast, cervical and lung cancer data sets; it investigated a number of proposed techniques for the analysis of skewed cost data and methods for data with incomplete patient follow up.

The aim of this final chapter is to pull together and summarise the main findings of thesis and to draw some broad conclusions about the methods and practice

of costing cancer. In doing so the contribution of the thesis to the area of costing and cancer is highlighted. Finally, this chapter indicates potential areas of further research.

11.2 Findings and contribution of the thesis

Chapter 2 introduced the concept of economic costing as used by health economists. The methods, recommendations and guidelines related to costing were explored by way of a literature review, with the aim of informing the empirical part of the thesis. The literature review, in providing answers to four key questions: 1) What are costs, 2) Why are we interested in costs? 3) How are costs estimated? and 4) How should costs be analysed?, has presented a descriptive outline of how the process of costing ought to be undertaken and how the issues related to costing be handled. The methods and guidelines were separated into three broad categories; current accepted conventions; debateable issues and; emerging techniques requiring further empirical research. It is interesting to note that approximately one-third of all methods and issues reviewed were deemed to fall under the heading of 'current accepted conventions'. This is unsurprising given that costing by health economists has only been undertaken to any great degree throughout the past three decades. Therefore like other areas in health economics is an evolving discipline.

Chapter 3 reported on a systematic review of the literature on costs and cancer. It was useful for the basis of the design of the empirical work in the thesis. The search resulted in 262 studies on cost and cancer, of which 50% were considered to be simply costing studies, 34% were cost-effectiveness analyses, 12% were cost-utility analyses, 2% cost-minimisation studies and 2% cost benefit analyses. Forty eight per cent of the

studies were conducted in the US while 12% were UK based studies. It was unsurprising to find that most of the work had been conducted on cancer sites that display the highest incidence in the western world or are those amenable to early detection through screening, namely breast, colorectal, cervical, prostate and lung. In chapter 2 it was noted that there were some areas of accepted conventions in costing. However, the detailed review of forty published papers testified that in practice variation in the methods used exists even within a single disease classification such as cancer.

Chapter 4 outlined the methods used in the core costing chapters. The key messages from this chapter are as follows:

1. The time and effort involved with conducting a detailed retrospective cost analysis of this size is quite considerable. Economic evaluations are increasingly being conducted alongside trials. Although this enables resource use data to be collected prospectively, invariably researchers need to return to the patient medical notes to ascertain detailed patient specific resource use information. Investigating a disease such as cancer requires information on a number of interventions, chemotherapy drugs, radiotherapy planning and treatment, surgery, inpatient stays, diagnostic procedures and outpatient visits. This information, in such detail required for accurate costing, can only be obtained from patient medical notes.
2. Even where databases exist, for example cancer registry data, the data have not been collected for the purpose of costing and are therefore of limited use. There may be problems with completeness and misclassification of cancers by the registry as was confirmed by the work undertaken in this thesis.

3. Access to and use of patients' medical notes represents a problem for researchers in a number of ways:

    a. It is becoming increasingly difficult to obtain permission to access information in patients' medical notes. Recent guidance, with the intention of protecting patients' confidentiality, from the General Medical Council(1) and the House of Commons in the Health and Social Care bill(2) prevents researchers gaining access to medical notes unless for the purpose of audit. This will present problems for health economists in obtaining detailed patient specific resource use information for future research.

    b. Even when given permission to access the notes there are often problems of legibility, missing information (details of treatments, pathology reports or in the case of cancer; stage is rarely documented), destroyed notes (notes for patients who have not been seen in the last eight years can be destroyed) or there may be a financial cost in accessing the notes of patients who have not been seen in the past eight years as they are invariably held off the hospital site in storage.

Chapters 5-7 have reported on the results from the empirical estimation of the hospital costs of breast, cervical and lung cancer in the Trent region. The comparison of the cervical cancer management costs with those of lung and breast cancer clearly indicates not only that the former are significantly higher but that the implications of stage progression for management costs differ between cancer sites.

In all three cancer sites the standard deviations of the mean costs emerged as particularly high, indicating the wide variation in patient-specific resource use even within a given stage at diagnosis.

Chapter 8 explored the appropriate statistical analysis to test for the difference in mean cost according to disease stage using the breast, cervical and lung cancer datasets. Cost data are invariably skewed and according to statistics textbooks, parametric tests should not be used in these circumstances. A number of proposed techniques have been suggested for the analysis of skewed cost data; removal of outliers, transformation of the original data, use of nonparametric tests and bootstrapping. However, the use of these methods made no difference to the results estimated using parametric one-way analysis of variance and t-tests. Following this finding this chapter resulted in a number of conclusions;

1. The reporting of the distributional form of the data is of importance, this can be done using standard descriptive statistics or by displaying the data in a histogram.
2. The arithmetic mean value of the cost data should always be reported, as this is the value health economists require when calculating cost-effectiveness ratios, and is also a necessary requirement for the estimation of the total cost of providing a package of care or intervention.
3. It is acknowledged that parametric tests are sufficiently robust to accommodate deviations from the assumptions underpinning them. However, the bootstrap method can be used as a check for the use of such parametric tests.

Chapter 9 explored the analysis of costs where data are censored. Censored cost data occurs where the end point of interest has not been observed for a particular

individual/patient. Several techniques have been proposed in the literature that aim to adjust for any censored data when estimating the average total cost. These range from ignoring the issue of censoring altogether to estimating costs based on only those with complete cost histories to using a combination of cost and Kaplan-Meier survival estimates that takes account of any censoring. The chapter reported on the results for the breast and cervical cancer data using the proposed techniques. Unfortunately from these results and the limited empirical publications on the use of analytic methods for censored cost data, it is impossible to make any firm conclusions at present. The existence of censoring does present real methodological and practical problems for the estimation of mean total costs. However it is too early to tell whether, the methods proposed do actually make a difference to the results, moreover, it is currently unclear how to best judge between the techniques. The results obtained in this chapter are limited to a specific disease, it may well be that one would get different results from the analysis of censored cost data for different diseases or interventions.

One important conclusion that can be drawn from this chapter is that, when undertaking any analysis of cost data, information on the number and proportion of patients with complete and censored costs should be routinely reported along with the method used to take account of the censoring.

Chapter 10 is a discussion chapter, where the empirical findings of the thesis are discussed in relation to three important areas. Firstly, how the experience of costing in practice complies with the principles of costing set out in the guidelines. Two areas of divergence were indicated and their strengths and limitations in relation to use in this thesis discussed; the use of a narrow hospital based perspective compared with the

recommended societal perspective and the use of average costs in place of true opportunity or marginal costs. The second discussion topic centred around the possibility of collecting the data for this thesis at a lower cost. The final area for discussion looked at the potential users and policy implications of the cost results.

11.3 Future research

The research in this thesis has highlighted a number of potential areas of future research:

1. This thesis has limited its exploration of the cost datasets to univariate analysis, in particular how the cost of cancer varies according to the stage at diagnosis. However, the estimation is more complicated as variations in the cost of treatment are not only due to differences in stage at detection but may also be affected by other factors which cause the basis or prognosis of disease to differ between patients. Moreover, the estimate may be complicated by differing follow up times and incomplete data. Hence, there is a need to explore the cost datasets further using multivariate regression techniques that allow for longitudinal analysis with the presence of censored cost data. This analysis will also provide information on the main predictors of cost. This type of analysis has been undertaken for other disease area such as stroke(3).

2. The second area of future research lies in estimating the impact that early detection programmes have on the total treatment costs of cancer. Two new screening programmes have been mooted; screening for lung cancer

using CT scanning and HPV screening. The lung and cervical cancer treatment probability and cost data estimated in chapters 7 and 6 could be used within a Markov model to provide estimates of the cost-effectiveness of such screening programmes. Preliminary work on a Markov model for lung cancer screening has recently been undertaken using Canadian data(4).

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