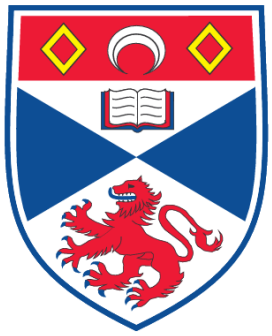
EVALUATION OF HEALTHCARE MANAGEMENT ISSUES IN THE PROVISION OF CLINICAL SERVICES FOR FAMILIAL BREAST/OVARIAN CANCER

Marta de Azevedo Moreira Reis

A Thesis Submitted for the Degree of PhD
at the
University of St. Andrews



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Abstract

Despite there being pragmatic national guidelines for assigning risk to women with a family history of breast cancer, the evidence base is still sparse. There are three major questions: First, how can an assignment of "low" risk be made most efficiently? Second, what are the actual outcomes for higher-risk women enrolled in special surveillance programmes? Third, what are the costs and benefits of current management of members of breast cancer families?

My thesis reviews the evolution of clinical services for familial breast cancer and the existing literature in the field. I describe the gathering of information from the service records of the Tayside Breast Cancer Family History Clinic and from specific research exercises that involved collaboration with other centres in the UK and abroad. My findings are as follows:

1. Histories provided by the families are not sufficient to assign risk accurately. They must be extended and verified from other records by clinical geneticists. Women assigned a low risk can be informed by post, but some may require further support. The 2004 NICE guidelines for assigning risk are fairly accurate, but may under-estimate it for some women aged 45–55 years.

2. Annual screening of young women at increased risk results in detection of most cancers at a curable stage. Women who carry BRCA1 mutations fare less well, even when tumours are detected at an apparently early stage.

3. Costs of accurate risk assessment are outweighed by savings from the better targeting of surveillance programmes. Early cancer detection in young women enrolled in these programmes achieves a substantial gain in life expectancy at a cost of £3,700 per quality adjusted life year (QALY). Prophylactic surgery for carriers of BRCA1 mutations is highly cost-effective.

The thesis concludes with a discussion as to how these findings might be extended and clinical practice improved in the future.

Declarations

I, Marta de Azevedo Moreira Reis, hereby certify that this thesis, which is approximately 63,000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

Date: 11/12/2006

Signature of Candidate

I was admitted as a research student on 25th September 2000 as a candidate for the degree of Doctor of Philosophy in November 2000: the higher study for which this is a record was carried out in the University of St Andrews between 2000 and 2005.

Date: 11/12/2006

Signature of Candidate

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Doctor of Philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Date: 11/12/2006

Signature of Supervisor

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Date: 11/12/2006

Signature of Supervisor

Copyright declaration

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To you my husband, Luke, with your love, patient tolerance of my long hours and support both emotionally and intellectually and to our little daughter for her love and understanding I cannot thank you both enough for all this.

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There were trying moments during the course of my work starting with the sad loss of Professor Mo Malek as my second supervisor on the Management side of this work.

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O que me preocupa não é o grito dos maus mas o silêncio dos bons

Martin Luther King

List of abbreviations

BSO Bilateral salpingo-oophorectomy

CASH Cancer and Steroid Hormone study

CSO Scottish Executive—Chief Scientist's Office

DCIS Ductal carcinoma in situ

ER Oestrogen receptor

FEC 5-Fluorouracil, epirubicin, cyclophosphamide

FIGO International Federation of Gynaecology and Obstetrics

FNA Fine-needle aspiration

HMO Health maintenance organisation

HNPCC Hereditary non-polyposis colorectal cancer

HRT Hormone replacement therapy

ICER Implied incremental cost-effectiveness ratio

ISD NHS Information Services Division

MARIBS Study Magnetic Resonance Imaging Breast Screening Study

MRI Magnetic resonance imaging

NBSP National Breast Screening Programme

NICE National Institute for Clinical Excellence

NIS Norwegian National Insurance Service

OCCR Ovarian cancer cluster region

PBMA Programme Budgeting and Marginal Analysis

POHEM Statistics Canada—Population Health Model

PROSE Prevention and Observation of Surgical Endpoints

QALY Quality Adjusted Life Year

SIGN Scottish Intercollegiate Guidelines

TAYREN Tayside Primary Care Research Network

TRAM flap Transverse rectus abdominus myocutaneous flap

WLE Wide local excision

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Chapter 1

Introduction

1.1 Breast cancer: its causes and management

The oldest recorded information about breast cancer was from ancient Egypt; tumours and treatment were described in at least three papyri dated from 1600 BC: the Ebers, Smith and Petrie papyri.[2] Edwin Smith in 1862 discovered the papyrus (Smith Papyrus) that recorded eight cases of tumours of the breast that were treated by cauterisation using what was called the "fire-drill",[3] as was common practice in Egypt.

At the time, surgery was used in cases without any form of anaesthesia or antisepsis and, more often than not, the patient would either die from the crude procedure with continuous bleeding or from infection afterwards.

Gradually the disease became more familiar to physicians and its treatment has developed throughout the centuries. Andreas Vesalius, during the Renaissance, recommended mastectomies with ligatures of the bleeding areas to control blood loss.

A physician called Le Dran first recognised that breast cancer could spread to regional lymphatic tissue. This was a major development in the understanding of the disease.

Only in the mid-1800s did surgeons begin to record details about their cases of breast cancer. The common treatment at that time was complete removal of the breast gland and lymph nodes in an attempt to avoid further disease development in the area. Radical mastectomies with total removal of the regional lymph

nodes were commonly carried out, including removal of the pectoral muscles, leaving the patients with wounds that were difficult to heal and the stigmata of this aggressive surgery.

Oophorectomies were introduced as part of breast cancer treatment towards the end of the nineteenth Century by Beatson in Glasgow as a means of restraining uncontrolled growth of tumours in the breast. It was the first time that hormone therapy was used in the management of any form of cancer.[4,5]

Survival rates began to improve at the beginning of the 20th century, with notable advances during and immediately after the Second World War. Ten-year survival rates following mastectomies were around 10% in the 1920s; this improved to about 50% in the 1950s. The figure is still gradually improving as new methods of detection and treatment become available.

Breast cancers are traditionally classified according to tumour size (T), nodal involvement (N) and the presence or absence of distant metastases (M) as shown in Table 1.1. This classification can be correlated with the staging of the disease as in Table 1.2.

Table 1.1: TNM classification of breast tumours

T_0	Cancer in situ
T_1	≤ 2 cm
T_2	2–5 cm
T_3	> 5 cm
T_4	Involvement of chest wall and/or skin, and/or inflammatory cancer
N_0	No regional node metastases
N_1	Palpable mobile ipsilateral axillary nodes
N_2	Fixed involved ipsilateral axillary nodes
N_3	Ipsilateral internal mammary node involvement
M_0	No evidence of metastasis
M_1	Distant metastasis

Table 1.2: Correlation of UICC staging and TNM classification of breast cancers

UICC stage	TNM classification
I (early)	T_1, N_0, M_0
II	T_1, N_1, M_0; T_2, N_{0-1}, M_0
III (locally advanced)	Any T, N_{2-3}, M_0; T_3, any N, M_0; T_4, any N, M_0
IV (advanced)	Any T, any N, M_1

With better understanding of the disease and better data collection, clinicians and scientists developed new treatments based on clinical trials. It was then that staging systems were developed, dividing breast cancer patients into groups according to clearly defined clinical signs of the disease. It became clear that the earlier a breast cancer was diagnosed and treated, the better the patient's chance of long term disease survival (reviewed by Dixon[6]).

In the 1970s, interest in the molecular basis of human cancer expanded enormously with the emergence of techniques for DNA analysis and manipulation. Researchers at the University of California, were among the first to report that certain genes in the normal cells of the body could somehow become abnormal ("transformed") and could therefore spur cancerous cells to grow[7–9] and that the growth regulation of the cell involved a complex chain of events from extracellular regulators interacting with the cell plasma membrane and thereafter mediators in the cytoplasm would transmit signals from the plasma membrane to the nucleus where they would control DNA-binding proteins.

The transformed cell would be unable to respond to regulatory signals and therefore the cells would grow without control.[10]

In 1975, Dulbecco was one of the first to advance the hypothesis that, if the growth regulators specific for the aberrant behaviour of cancer cells were to be identified, they could be used for stopping the growth of the malignant cell.[7]

Others have pointed out, that most carcinogens are promutagens (generating mutagenic substances that induce cancer) so that a reduction in the incidence of cancer could be achieved by the identification of promutagens and their elimination from the environment.[11]

1.2 Familial breast cancer

The evolution of a tumour cell clone involves a series of oncogene activations and tumour suppressor gene inactivations, each of which will confer some phenotypes on the cancer cell, the sum of these phenotypes constituting malignancy.[8]

Thereafter, it became clear that inherited mutations in growth-regulatory genes could account for some familial cancers though, in fact, this had been predicted

as early as 1914 by Boveri.[12] As is often the case, that work was so far ahead of its time that it lay largely neglected for some seventy years.

A striking feature of breast cancer occurring in obvious family clusters is early age of onset, often with presentation before age 40. In the 1990s, Hall and colleagues[13,14] mapped the first gene linked to major early-onset breast cancer risk (BRCA1) to chromosome 17q.

The finding was rapidly confirmed by Steven Narod et al.,[15] who showed that the locus is also linked to predisposition to carcinoma of the ovary. It is thought that this gene is responsible for 2–4% of all breast cancers and 5–10% of ovarian cancers[15] and that individual mutation carriers are at increased risk for both breast cancer and ovarian cancer.[16]

The BRCA1 gene was isolated and characterised three years after the locus was mapped.[17] It is large, with twenty-four exons spanning over 100 kilobases of DNA and bears very little homology to any other known genes.

Female carriers of mutations in this gene experience a high lifetime risk for developing breast cancer (as high as 85–90%, compared to an 11% risk for the normal female population who do not carry the faulty gene). It was confirmed that they also have a high risk of ovarian cancer (variously estimated at 35–60%). Though familial ovarian cancer is less clearly associated with early age of onset than familial breast cancer and very rarely presents under the age of 35 years.[18]

In 1994, a second breast cancer susceptibility gene was tracked down to chromosome 13q12–13 and was called BRCA2.[19] It was cloned and characterised the following year.[20] This gene is even larger than BRCA1 with twenty-seven exons and the two genes show almost no sequence homology. In contrast to BRCA1, male breast cancer cases are relatively common in BRCA2 mutation families but the risk for ovarian cancer is lower (27%). However, mutations in the central part of the BRCA2 gene appear to carry a high relative risk of ovarian cancer (hence the term ovarian cancer cluster region – "OCCR").[18–21]

Searching for BRCA1 and BRCA2 mutations is a major task because the genes are so large and the cost and effort involved in the analysis will require strict criteria for screening. The likelihood that a germline mutation is present in one of the genes is simply derived from the family history that should have been verified.[22]

The very large Cancer and Steroid Hormone (CASH) model study, in the USA, was a population based, case-control study that estimated the proportion of breast and ovarian cancer cases in the general population that were likely to be attributable to mutations in breast/ovarian cancer genes. In the general population, it generated estimates of approximately 10% of ovarian cancer cases and 7% of breast cancer cases as being in carriers of a breast/ovarian cancer susceptibility gene.[23,24]

There are several clues to raise the suspicion that an individual may be carrying a mutation in one of BRCA genes, for example: early age onset of breast cancer, bilateral disease, history of both breast and ovarian cancers in the family with several cases of breast and/ or ovarian cancers, the presence of male breast cancer and Ashkenazi Jewish background (because certain inherited mutations in both BRCA1 and BRCA2 occur with high frequencies in this population group[18]).

The Breast Cancer Linkage Consortium[25] found that overall some 52% of families with at least four cases of breast cancer are linked to BRCA1; 32% linked to BRCA2 and 16% to neither gene. The majority of the breast-ovarian families were attributed to BRCA1 mutations (81%) and most of the others due to BRCA2 (14%) while the majority of families with female and male breast cancers were due to BRCA2 (76%).[18]

Tumours in BRCA1 mutation carriers have some distinct features that characterise their disease aggressiveness. They are mostly aneuploid, with a hyperdiploid DNA index and high S-phase fraction, indicating rapid proliferation. Those tumours tend to be of high nuclear grade and also have a deficit of DCIS (ductal carcinoma in situ) around the invasive tumour and tend to show significant lymphocytic infiltration, yet may metastasise to distant sites before regional lymph nodes are involved. They are almost invariably oestrogen receptor and progesterone receptor negative. BRCA2 tumours may show similar features but to a lesser degree and, in general are pathologically more heterogeneous.[26]

The medullary or atypical medullary carcinoma types are found more frequently in BRCA1 than in BRCA2 mutation carriers. The review of pathological findings from breast cancer families (though some of these cases are almost certainly sporadic) in the Breast Cancer Linkage Consortium study suggests that the cancers due to BRCA1 mutations have a different natural history when compared to BRCA2-related and sporadic cancer cases, with potentially different

implications for the management of the disease as well as for the surveillance programmes.[25–27]

Sporadic cancers (not inherited) are defined as the remaining cancers that are not due to "high penetrance" defects in genes such as BRCA1 or 2, though they may include cancers with genetic "low penetrance" defects.[28] Penetrance in this context is defined as the probability of disease development in individuals who carry a mutation in a breast cancer predisposing gene.

Other genes linked to breast cancer have since been discovered and further searches for "BRCA3" are under way as there is a strong possibility that it accounts for other forms of familial breast cancer.[29] There are several familial syndromes associated with breast cancer, as illustrated in Table 1.3.

The fundamental cause of breast cancer is still unknown: prevention is still not possible and further research is currently being carried out to enable better understanding of the disease process and pathways that may lead ultimately to prevention. The currently available dietary or pharmacological forms of intervention may reduce the risk of breast cancer but total prevention will only be possible when full understanding of the disease process is achieved.

1.3 A short history of "breast cancer family history" clinics

From the late 1980s, there has been growing recognition of the need to identify women at increased risk and to offer them close surveillance. As indicated above, there is evidence that most high penetrance inherited breast cancer is characterised by early onset of the disease, so that only a few families will have a predisposition to later onset disease.

Breast cancer genetics clinics were introduced with the purpose of identifying those at increased risk and referring them to breast specialists for regular surveillance.[32,33] Such programmes have been widely adopted but many have evolved from research projects and service provision in the UK was not structured, from the outset, in a uniform way. On a Europe-wide scale, provision has been even more diverse.[34]

Table 1.3: Common familial syndromes associated with breast cancer[22,30,31]

Syndrome	Features
Li-Fraumeni	Classically composed of early onset breast cancer; soft tissue sarcomas in childhood, acute leukaemias, brain tumours and carcinoma of the adrenal gland. Gene involved: TP53. Autosomal dominant syndrome; multiple primary tumours characteristic. Li-Fraumeni-like syndrome sometimes involving CHEK2 gene.
Gorlin	Multiple naevoid basal cell carcinomas; dental and bone cysts and other skeletal malformations. Mental retardation can also be found; possible excess of ovarian cancers and increased frequency of breast cancer. There is also an increased risk of medulloblastoma / astrocytomas. Autosomal dominant; gene PTCH mapped to 9q22-31.
Site-Specific breast cancer	Males are occasionally affected and no excess of cancers other than breast is noted. Autosomal dominant: gene involved: BRCA1 and BRCA2. (Same genes implicated in familial breast/ovarian cancer. Absence of ovarian cases in some families unexplained: may simply be chance)
Cowden disease	Multiple hamartomas of skin and oral mucosa. Other organs are also affected by adenomas mainly: thyroid, GI tract and CNS. Palmar pits are noted. Autosomal dominant. Breast cancer in up to 50% of women affected and thyroid cancer in 10%. Gene involved: PTEN on chromosome 10.
Peutz-Jegher	Syndrome characterized by hyperpigmentation, mainly in and around the mouth; multiple polyps in the small intestine and some excess of colorectal and other cancers (includes breast and ovarian cancers). Gene involved: STK11 mapped to chromosome 19p. Autosomal dominant.
Ataxia Telangiectasia	Syndrome characterized by progressive cerebellar ataxia, telangiectasia mainly of the conjuntiva, immunological defects. Increased risk of other malignancies, typically leukaemias. Autosomal recessive syndrome, gene ATM on chromosome 11q. Female heterozygotes may have increased risk of breast cancer.
Muir-Torre syndrome	Skin lesions (sebaceous adenomas and keratoachanthomas) are associated with colorectal, laryngeal or duodenal cancers. There is some excess of breast, ovarian bladder and uterine cancers, Gene involved: MSH2, MLH1. Autosomal dominant. Overlap with other RER (replication error repair) gene syndromes.

There is a great need to evaluate the different models and to establish an evidence base on which to make recommendations for the most acceptable and cost-effective protocols for ascertainment and management of women at high risk of breast cancer. This need was spelled out in the 1996 Report of the Working Group on Genetics and Cancer[35] that presented the first national (UK) recommendations for the scope and organisation of the services for breast (and other) cancer families.

Data are therefore being collected to provide an evidence base for the kind of surveillance or intervention that should be offered, the levels of familial risk that justify such surveillance/intervention and the ages at which programmes should be initiated and discontinued. The present study is a contribution to these ends.

In the UK, breast cancer genetics clinics were introduced in the late 1980s.[32,33] Manchester was the first centre to introduce a structured clinic for the identification of patients at risk and provision of a surveillance programme. However, in Dundee, a breast clinic had been set up by Professor Sir Alfred Cuschieri and Mr Robert Wood as early as 1977.

Data on family history of breast cancer were collected prospectively on each patient attending the Tayside breast service for any reason and those recording a positive family history were kept on regular surveillance thereafter, even if the original reason for referral was satisfactorily dealt with.

It is important to highlight that at this point there was no input from genetics colleagues in evaluating the level of risk for each individual with a family history of breast cancer and therefore, in many instances, the reported family history would not satisfy criteria currently used by geneticists for assessing patients' individual risks.

Nevertheless these surgeons were true pioneers in the field as for over 17 years women were kept on regular surveillance based on the *limited* information about their family history given at the original (symptomatic) consultation. With hindsight, of course, resources available at that time were not accurately targeted and doubtless there was some unnecessary exposure of well women to procedures that could lead to complications.

In 1994, Mr Paul Preece, in association with Prof Michael Steel, geneticist from St. Andrews University and Dr David Goudie geneticist at Ninewells Hospital,

introduced the first structured joint family history clinic in Tayside. The aim of the clinic was to investigate the patients with a family history of breast cancer who had been on regular follow up since 1977 (accounting for approximately half of all attendees), as well as new referrals, and to assess their actual risk for inherited breast cancer using new predictive models.[23,24,36]

With increasing awareness of the importance of family history in determining individual risk for breast cancer, the number of new referrals escalated, with a few patients initiating the referrals themselves or patients being advised by a clinician to seek guidance on the management of familial breast cancer. As a result, a long waiting list developed rapidly for patients to be seen at the clinic.

In 2000, Eccles et al.,[37] on behalf of the UK Cancer Family Study Group, recommended, in line with the 1996 Working Group Report, that women referred to those clinics but thought not to be at substantially increased risk for breast cancer could in fact be seen by GPs and reassured of their "low" risk status, while only "high risk" women should be seen by geneticists. In this context the term "low risk" is based on categories also defined in other widely adopted guidelines (e.g. SIGN 1998[38] and more recently, NICE 2004[39]). It refers to women whose family history places them at lifetime risk for breast cancer estimated at less than 1.7 times that of the general female population. Such women are not considered to require special counselling nor clinical/mammographic screening, beyond that provided by the National Breast Screening Programme from the age 50 years. The 1996 Working Group did, however, emphasise the need for these women "to receive accurate risk information in a sensitive and supportive manner". Of course, implementation of selection and reassurance at Primary Care level would require the GPs to be knowledgeable in cancer genetics and able to undertake full assessment of the patient's risk. However, by this time, evidence was beginning to accrue – and has subsequently become overwhelming - that GPs felt insecure in their "gatekeeper/counsellor" role and that a high proportion of onward referrals to specialist services were of women whose genetic risk fell below the guideline "threshold" for enrolment in surveillance/intervention programmes.[40–47]

In the face of the growing demand and the apparent impracticability of "first stage" screening at Primary Care level, a need for some reorganisation of the Tayside clinic was recognised and in 1999, funds were granted by the Scot-

tish Executive (CSO) to examine the feasibility, acceptability and efficacy of a "postal" means of establishing which referral patients were in fact at low risk, then reassuring them of that without the need for a formal clinic appointment. This would free up clinic time and personnel so that "moderate" and "high risk" women could be seen more promptly and have their surveillance programme discussed and initiated.

That the issues faced in Tayside were not unique to that centre was shown in a UK- wide study, to which Tayside contributed, of clinical provision for women at increased genetic risk of breast cancer.[45]

In general, regular surveillance in UK clinics is offered until age 50 years (genetic risks by then will have declined) and thereafter participation in the National Breast Screening Programme is encouraged. However, some of the women will still have significantly increased risk beyond age 50 years, perhaps justifying alternation of cancer family clinic surveillance with the National Breast Screening Programme (i.e. an 18 monthly screening schedule), though practice in this regard is not uniform across the UK.

Tayside also participated in a programme that ran in parallel with the Breast Cancer Linkage Consortium, in which several European countries gathered and shared essential information on the provision and evaluation of services for women at risk of familial breast cancer. This was the 1996-1999 BIOMED 2 Demonstration Programme on Clinical Services for Inherited Breast Cancer, funded by the European Commission and co-ordinated from Scotland.

After collection of data from ongoing collaborative prospective studies, the Demonstration Programme reported on the outcome of early diagnosis and treatment of inherited breast cancer as measured by screen detection and interval cancer rates, stage and survival after diagnosis. Consensus recommendations for close surveillance of the women at "high risk" were offered, based on the findings of this programme, which still continues as an informal collaboration. This is discussed more fully in later sections.

The high risk women should be offered genetic counselling, education in breast self examination (breast awareness) and regular annual mammography as well as regular breast examination by a breast specialist from around the age of 30 years or five years before the youngest case onset in the family.

From the age of 50 years, mammography would be performed every second year for those still at significant risk or at eighteen monthly intervals, alternating with a local population-based breast screening programme. It was also suggested that BRCA1 mutation carrier patients may benefit from even more frequent examinations and that their cancer risk could be reduced further if they underwent prophylactic oophorectomy at around 40 years of age.

There are still some controversies, for example, in relation to frequency and mode of screening and the role of prophylactic mastectomy for BRCA1 mutation carriers since, as discussed later, the most recent data from the European collaboration confirm earlier suspicion that these patients fare poorly (compared to BRCA2 mutation carriers or those with no demonstrable mutation) even when tumours are screen-detected and at an apparently early stage.[48–50] The effects of all such interventions need to be well documented so that management strategies can be matched more accurately to individual estimates of risk.[51]

Screening the general population before age 50 years is unlikely to be cost-effective and the reason behind it is that the pick-up rate of early breast cancers would fall below the normal target of 6 per 1000 investigations. The presumption is that this would not apply to a highly selected group such as the "high/moderate" risk women.[22]

The increase in demand for genetic services is probably a reflection of women's concerns about familial breast and/or ovarian cancers in view of a media release of scientific information with, as a result, an incomplete understanding of the interventions available as well as poor understanding of genetic testing as pointed out by Nelson and colleagues.[52]

Health care organisations are responsible for both management and delivery of healthcare to a population, meeting its needs in the best possible way under the current constrains of resource allocations. Priority setting has been part of this process, in view of the need to make choices on funding of services, known in the UK as "commissioning of services".[53]

Political and/or historical patterns influence centralised resource allocation, which may contribute to sub-optimal use of the scarce resources.[54]

In order to set priorities in a health care system, as described by Mitton and Donaldson,[53] at least two key economic principles should be applied: one is

opportunity cost (defined as "the health benefits lost because the next-best alternative was not selected"[55]). In other words, it compares the relative (financial) benefits of alternative strategies. The second one is *margin*, which essentially means the difference between incremental cost of a new drug or procedure and the incremental gain (again in cost terms) to the health care system. Both are relevant to measuring the costs and benefits of a given intervention or task. They should help decision-makers to balance the costs and benefits of any proposed changes by placing a "price tag" on any proposed "shift or change in the resource mix".[53] The price tags attached to all proposed innovations can then be considered along with their potential health benefits in setting priorities for the allocation of limited resources within the NHS, or any other health care system. In principle, this should allow a fair assessment of the competing claims of such diverse objectives as increasing numbers of community midwives or provision of a new MRI scanner for a given population.

One of the approaches used in priority setting is called "Programme Budgeting and Marginal Analysis" (PBMA). It uses an advisory panel in charge of identifying areas of service growth and areas of resource release ("cut back") in order to fund the proposed growth within a given budget.[56] Over recent years it has gained a lot of credibility in the transparency of priority setting processes.

Choices in most areas of health care have become much more extensive in recent years. Cancer prevention, and specifically provision of cancer genetics services, illustrate this very clearly. As discussed earlier, there is a widely perceived need to develop high quality cancer genetics services and to get those services integrated into the healthcare systems.[57] Health economic evaluation of cancer genetics services should address issues of costs and benefits of the services to the community. They cannot simply be provided uncritically in response to demand.

Existing guidelines, outlined above and discussed in detail in later chapters, provide a starting point. However, the scale of service provision is in constant change and this needs to be reviewed regularly so that, if there is a benefit from a given service with efficient use of resources, expansion of service provision can be considered. This would imply constant re-evaluation of health economic issues.

With the existing gap between what the NHS can provide (with current levels

of funding) and what it could provide if more resources were available; priority setting is paramount to enable quality of care for all, as quoted by Professor Peter Baylis on behalf of the Royal College of Physicians Working Party[58] on the prescribing of costly medicines.

The demand for access to genetics services has exceeded their availability and, as a result, the NHS had to set priorities to achieve equity of healthcare provision within this field. Rationing is one of the key options available to the government when dealing with NHS budgets. Cost of treatment is clearly a necessary consideration when resources are limited.

Since the early 1990s, there has been an increase in reforming health care programmes in many European Countries and in the United States in view of the need to restrict costs "as there are fears that health services that are publicly funded may be inundated by demands for services that could be both inappropriate and excessive".[59] The NHS services in the UK have been affected in the same way, as Elliot and Popay[59] have described in their study looking at how policy makers apply evidence in the NHS. Many of the service reforms in this country coincided with further interest in evidence-based practice.

Decision-making processes should be based on the best evidence of practice currently available. Priority setting in health expenditure should be based on research evidence looking at differences between interventions, in terms of effectiveness, in order to make a service more responsive to the users.[59] These authors were concerned with how policy makers used research that was considered by them to be relevant to their own work. One of their case studies of interest to this thesis looked at an initiative to incorporate existing knowledge into guidelines for best practice for both commissioners and health providers using decision analysis, but also monitoring the influence of those guidelines on decision-making processes. There was a move to create techniques for improvement of decision-making and, as a result, to promote dialogue between purchasers and health care providers. The authors also reported the monitoring and evaluation of a service's effectiveness. Agreed outcome measures were used in this exercise as one of the aims was to develop a model of setting and monitoring outcomes. One of their findings was that research could clarify and contribute to the decision-making process but was not there to provide answers to all questions posed. Research was just one of the many sources of informa-

tion used by policy makers during the process of decision-making, together with constrains on budget, national and local policy guidance. With the introduction of clinical governance and risk management in health care, there has been a drive for services to provide a standard of care that is transparent, sensitive and based on evidence of good effective practice. Risk management is an essential element, with the objective of assessment and reduction of risks or harms to the patient and staff involved in the delivery of given services.

Standards of service provision have been drawn up by the NHS and regular visits to each service are undertaken to evaluate how the local services are meeting all criteria set and to make sure that appropriate policies and procedures are being implemented. As a result, continuous quality improvement should be achieved, ensuring that effective operational frameworks are in place.[60]

1.4 Purpose and content of the work presented in this thesis

The purpose of the linked series of studies reported in this thesis is to evaluate the cost-effectiveness of current provision of risk assessment and surveillance for women who may be at increased genetic risk of breast cancer and hence to provide a constructive review of the current guidelines for management of familial breast cancer. The approaches taken include a randomised trial of "postal" risk assessment, an investigation of costs involved in the clinical service, plus measures of the detection rate for breast cancers and the clinical stage and outcome of these cancers, compared to an age-matched cohort of patients who had not been enrolled in any surveillance programme. They also incorporate studies designed to measure directly age-specific breast and ovarian cancer risks for women assigned to the "low risk" category on the basis of their family histories.

The work has involved:

1. Investigating the accuracy of risk assignment for women referred to the breast cancer family clinic, in relation to the effort expended in verifying and extending reported family histories: evaluating the economic and psychological implications of rigorous implementation of guidelines excluding "low risk" women from access to special surveillance.

2. Undertaking and documenting diagnostic procedures (clinical examination, standard mammography, extra mammographic views, ultrasound of the breast, FNA, core biopsies, open biopsies) for women in the familial surveillance programme and investigating the costs associated with these procedures.

3. Sharing data with colleagues from other European Centres on follow-up of patients enrolled in the surveillance programme and in whom breast cancer was subsequently diagnosed, in order to establish whether the aim of early detection was being achieved and to evaluate its efficacy in terms of reduced morbidity and mortality.

4. Sharing data with the same colleagues on the short- and long-term outcome of prophylactic mastectomy in women at high genetic risk of breast cancer.

5. Comparing the outcome (and associated costs) of breast cancer in young women (under 50 years of age) diagnosed at stage I (small tumours, node negative) or in later stages (bigger tumours, node positive) to assess the potential cost savings achievable through early detection of cancer (i.e. through "stage-shift").

6. Expanding through a Scotland-wide retrospective study, a Tayside pilot study of breast and ovarian cancer incidence in women referred to cancer family clinics, whose familial risk did not, according to current guidelines, place them in a high enough risk category for inclusion in surveillance programme – i.e. testing validity of the "threshold" specified in the current guidelines.

The work of Nelson and colleagues[52] was based on an analytical framework looking at interventions and, health outcomes of a population seeking advice on the issues of inherited breast and ovarian cancer risk. They have addressed several key questions that arise along the path followed by a woman with a family history of breast or ovarian cancer.

With this in mind, I have designed a similar analytical framework to address specifically the issues related to interventions available for those at increased

risk for the disease and also to evaluate the current guidelines for those services in this country (see Figure 1.1).

The series of 7 key questions in the framework are addressed through real 'hard' data from the Tayside familial breast cancer clinic and observational studies carried out during the course of my work, rather than the hypothetical approach adopted by Nelson's group.[52]

While the work I am reporting has involved many individuals and groups, I have personally taken either the lead or a substantial contributory role in all the above elements. The analysis of clinical implications and future directions is my own.

Are we managing the demand for genetic services well with the current available resources and provision of services facilities? Ideally, we should concentrate the efforts of regular screening for women at significant familial risk for breast and ovarian cancer, selecting carefully who should benefit most from regular screening at the specialist genetic clinics. For the high genetic risk group resources should be allocated to offer them genetic testing and risk reducing procedures in addition to regular screening. In other words, it would be important to demonstrate whether the provision of those services can produce benefits to justify the costs and not simply responding to the demand for the this type of service provision.

In an ideal setting, familial breast cancer genetic clinics should be evaluated by randomisation (i.e. randomise to get or not to get counselling and regular screening) but this would be ethically unacceptable and therefore follow-up observation analysis of patients has been used.

It has emerged from assessment of familial ovarian cancer services (by a similar process of follow-up and observation) that clinics for regular screening of women at significant genetic risk for the disease have not achieved their primary objective as they fail to detect cancers at early stages of the disease.[61] Conversely, in the case of breast cancer surveillance, there are indications that regular screening programmes for women at significant genetic risk for the disease can be effective in the detection of cancers in early stages and that the patients do well as a result of it. This is obviously a crucial issue and is the principal theme of Chapter 5.

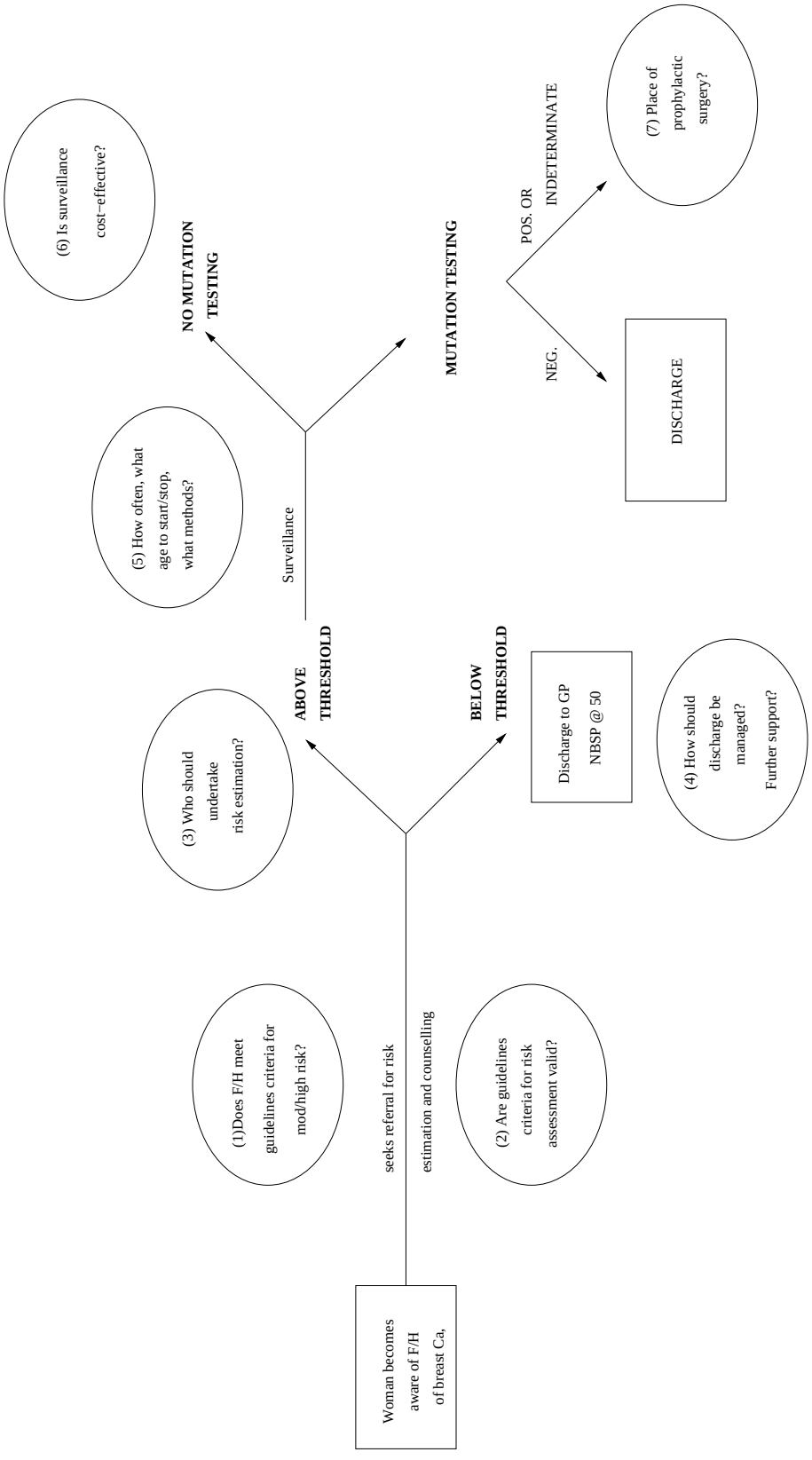

Figure 1.1: Analytical framework

While this encouraging conclusion seems to apply to the great majority of women with a family history of breast cancer, different considerations may apply to BRCA1 mutation carriers. Specifically, they may benefit less from regular surveillance so for them more effective interventions need to be examined. These may include prophylactic salpingo-oophorectomy, bilateral mastectomy or both as discussed in detail in Chapter 5.

MRI (magnetic resonance imaging) screening for those women may be more beneficial than mammographic and clinical surveillance but long-term evaluation of results will be required and is outside the scope of this thesis.

UK services concentrate on applying strict risk assessment criteria selecting those at "moderate" and "high" risk for regular surveillance but is the definition of 'moderate' risk valid? The Australian guidelines[62] define any breast cancer risk higher than normal population level as "moderate" risk, but they limit provision of surveillance to those at "high" risk so extending the definition of 'moderate' risk carries no cost implications. In the UK, to offer surveillance for women below the current risk 'threshold' could be expensive. The question then is what is the most cost-effective 'cut-off' level? That is the theme of Chapter 6.

These are some of the issues addressed in this thesis. Several will, require longer-term evaluation and further analysis which hopefully will be forthcoming through other work of this kind. Within this thesis, I am keen to identify areas that will provide enough evidence for review of the currently available guidelines. As I hope to demonstrate, genetic services, as currently organised within the NHS, can generate reasonably accurate measures of breast cancer risk, based on family history. They can also facilitate design, implementation and evaluation of preventive programmes aiming at the saving of both life and public money.

Chapter 2

Literature review

The literature review has been based on PUBMED search using the following terms:

"Cost effectiveness familial breast cancer clinics"; "familial breast cancer clinics"; "familial breast cancer follow-up clinics"; " management of familial breast cancer", "policy framework for cancer genetic services in the UK", "priority setting in health care" as well as by other relevant key words and individual researcher names with relevant linked papers.

2.1 Ascertainment of risk; guidelines and their implementation

Cancer genetics referrals have been on the increase in line with expanding knowledge of genes that can be linked to breast cancer and other cancers.[34,63] Selection criteria have been proposed, aiming at considerable reduction of inappropriate referrals by means of a 'filtering' system, retaining the ones most likely to benefit from preventive interventions.[64]

The need to identify individuals who are genuinely at risk for breast cancer has led to creation of multidisciplinary clinics, mainly on an ad hoc basis, with research funds. These clinics aim to counsel those at increased risk of cancer and to offer risk management to reduce mortality and morbidity.

However, the NHS is gradually incorporating these research-based clinics into new regular service provision; hence the continuing requirement for education and referral guidelines for primary care to identify individuals who require detailed assessment of their risk. There is a lack of consensus on how the cancer genetic services should be delivered and consequently there is a need for evidence to inform the developing service.[65]

The principal activities of such services embrace clinical care (remembering that most of the individuals seen in those clinics are healthy), registers of genetic conditions that will identify individuals at increased risk for the condition, education of both post- and under-graduates, research and audit.

Clinical genetics services deal with referrals of individuals seeking advice for a given condition, (in our case, breast and/or ovarian cancer) and certainly involve a considerable amount of time in the collation of information needed for individualised risk assessment, drawing of family pedigree and, of course, providing clinic consultation with those likely to benefit. The time taken to obtain all the necessary information should be considered by the services commission workforce and will be reflected in the costing exercise.

Policy makers and general practitioners have different views on definition of the role of GPs in implementing the so called "New Genetics" creating some tension between the two parts.[66] Transformation of the current practice to include new specialised roles and skills, including some level of genetic service provision within primary care, is seen by some as an answer to increasing public demand for genetic counselling.

Historically, regional health authorities were in charge of commissioning genetic services. However, this responsibility was devolved back to individual health authorities, meaning that commissioning of those services would be competitive, in terms of services purchasing decisions, between acute and local services.[64]

The practical remit of cancer genetics services is set by guidelines for risk assessment, commonly based on the number of affected relatives, age at diagnosis and closeness of relationship.[67–69]

A "close relative" means a parent, sister, brother, son or daughter, grand-parent, aunt, uncle, nephew or niece.[38] These criteria are virtually identical to those applied in England and Wales before publication of the NICE guidelines:[39] but see Table 2.2.

Table 2.1: Criteria for identification of patients for specialist genetic services that may indicate a moderate or high risk of inherited breast/ ovarian cancer in Scotland[38]

Breast	Three or more relatives diagnosed at any age Two close relatives diagnosed under 60 years of age Mother or sister diagnosed under 40 years of age Father or brother with breast cancer diagnosed at any age One close relative with bilateral breast cancer diagnosed at any age
Breast / Ovarian	One close relative diagnosed with ovarian cancer at any age and at least two close relatives diagnosed with breast cancer under 60 years of age One close relative diagnosed with ovarian cancer at any age and at least one close relative diagnosed with breast cancer under 50 years of age One close relative diagnosed with breast and ovarian cancer at any age
Ovarian	Two or more close relatives diagnosed with ovarian cancer at any age

Very precise risk assessment is not expected to be calculated in primary or secondary care settings but the health professionals should be able to utilise the simplified criteria in Tables 2.1 and 2.2 to allocate women to "low", "moderate" or "high" risk categories.

In 1999, NICE (National Institute for Clinical Excellence) was created, setting priorities in healthcare, appraising clinical and cost effectiveness of health technologies that the Department of Health have referred for assessment and making recommendations that are mandatory guidance to the NHS regarding what should be made available to patients (this also includes new drugs). The authors of the NICE guidelines[39,70] for the care of women at risk for breast cancer rightly commented that the designation as "low risk" (cancer risk less than 1.7 times greater than general population and less than 3% by age 50) could be somewhat misleading as those women still have a risk above the population level and might perhaps be led to believe that they will never develop breast cancer.

NICE guidelines for the assessment of familial breast cancer also recognised the paucity of solid evidence on which to base criteria for entry to counselling and surveillance programmes, stating that "validation of risk assessment models is

needed urgently".

There are some differences between the referral criteria still used in Scotland and those recommended by NICE. Notably, according to NICE, women with two or more close relatives diagnosed *at any age* would be at "moderate" risk. In addition, the "high" risk category specified by NICE is slightly broader, implying that more women would be eligible for molecular genetic testing. Table 2.2 shows the more recent criteria for designation of women as being at "moderate" or greater risk for breast cancer, according to NICE guidelines.

Table 2.2: NICE guidelines criteria for referral of women likely to be at 'moderate' or greater risk, meriting referral from primary care to secondary care in England and Wales

Breast cancer in females	One first-degree female relative diagnosed with breast cancer at younger than age 40 years Two or more first or second-degree relatives with breast cancer diagnosed *at any age* (if only two affected, one must be first degree)
Male breast cancer	One first-degree male relative with breast cancer diagnosed at any age
Bilateral breast cancer	One first-degree relative with first primary tumour diagnosed before age 50 (for bilateral breast cancer, each breast has the same count as one relative)
Breast and ovarian cancer	One first or second-degree relative with ovarian cancer at any age and one first or second-degree relative with breast cancer diagnosed at any age (one of the above should be a first-degree relative)

A referral would require at least one of the above criteria.

Ten per cent of women diagnosed with breast cancer report having a positive family history of the disease[71] and by no means all of these are at increased genetic risk, hence the need for explicit risk evaluation algorithms.

On the other hand, a proportion of women with affected relatives will belong to families with mutations in dominant predisposition genes including BRCA1 and BRCA2, which are thought to be related to about 5% of all breast cancer cases. Mutation-carriers are also at increased risk of other cancers (particularly ovarian) and it is estimated that their overall lifetime risk for cancer will be 3–8 times the population risk.

In the absence of known mutation status, familial risk will be substantially increased if the first-degree relative was affected at a very early age and /or had bilateral breast carcinoma. "Moderate risk" women will have a risk estimate for the disease of 2 to 3 times the normal population level.[72]

The first document recommending a strategy for the delivery of breast cancer genetic services in England was produced by a Working Group for the Chief Medical Officer,[35] chaired by Professor Harper, and was based on a three-tier model (primary care, cancer unit and specialist cancer genetics centre). Gene testing should only be offered by specialist cancer genetics clinics and undertaken after appropriate information and genetic counselling have been delivered and with specific consent.

If an unaffected individual has received a negative predictive test result, (that is, the individual does not carry a genetic mutation which was identified in her family) the risk of developing *inherited* breast cancer will be considered to be essentially zero and surveillance programme will no longer be required for the individual. Her risk will fall into the normal population range that is related to age and she will be invited to participate in the National Breast Screening Programme from age of 50 years.

As detailed in Section 2.2, in conformity with the Working Group Report, for England, it has been recommended that only "high risk" families should be assessed through specialist genetic services.[34,73] Those judged to be at "moderate" risk are to be referred to regional breast units for enrolment in surveillance programmes.

Scotland, however, follows a two-tier, rather than three-tier system, all referrals judged to be above "low risk" level (i.e. both "moderate" and "high risk" categories) being seen at the regional genetics centre en route to enrolment in a clinical surveillance programme. This reflects the structure of specialist services in Scotland where the populations served by regional breast units and regional genetics centres are virtually identical.

A review of currently available services in England in 2001 indicates that several aspects of the model suggested in the Working Group Report were still not fully implemented as there was considerable variation in workloads and waiting times across regions; some did not have the three-tier or indeed any structured model in place.[45] This is discussed more fully in section 2.2.

To date, no clinic policy has been established for low risk breast cancer patients who account for 25-40% of referrals to most specialist breast cancer genetics clinics.[45]

It is assumed that those patients will be "screened out" by primary care though, as pointed out earlier (page 9) experience shows that this does not happen and many reports now record GP's disquiet with their "gatekeeper" role in this situation and a need for clear guidelines for referrals and specialist community support identifying a model that facilitates the involvement of GPs but without increase of their workload.[40,74]

2.2 Structure of clinical services for familial breast cancer in the UK

Cancer Genetics services for England and Wales should be organised in a three-tier structure, according to the Working Group Report. Primary care doctors would reassure individuals at normal population risk. Cancer units would provide risk assessment and screening for those at moderately increased risk.

Specialist Genetics Centres would see only those patients who are potentially at high genetic risk, for risk assessment, confirmation and extension of family history, detailed genetic counselling about their risks (and perhaps those of other family members) with provision of information relating to genetic aspects of cancer and above all, how this would be communicated to them.

Discussion of options for intervention to reduce the threat of breast cancer would also include the implications of molecular genetic testing for those at "high" risk. Support is needed for referred women all the way through the process of risk assessment and counselling by the specialist genetic centres.

Any living affected relative willing to give a blood sample for genetic testing could be identified and contacted. From the counselling point of view, it is also important to identify individuals who, as a result of an underlying mental health problem, might not benefit from genetic testing and those who may need to be seen at a specialist psychological service because of the actual or potential impact of test results.

Specialist genetics services would be linked to the specialist cancer centres, each serving a population of 1–2 million and would ideally have a consultant trained in both oncology and genetics with the support of nurse specialists, to deal with high risk individuals.

In England and Wales, except for women who can give a clear account of a "high risk" family history, the model used for evaluation of genetic risk, relies strongly on GPs and surgeons in Regional Breast units.

In Scotland, as noted, a different model was proposed, (with no second tier). Regional genetic services would support the surveillance units and primary care by providing genetic counselling both centrally and in outreach clinics.[72] In Northern Ireland the service is based on the Calman-Hine three-tier scheme but is developing centralised referral mechanisms similar to Scotland.[75]

David Wonderling and colleagues[45] described the cancer genetics services in the UK in a 1998 survey of 22 regional cancer genetic services recording how they are delivered in different regions. There is a wide variation among the regions of the UK in provision of services, with referral rates being higher in centres providing mammography directly and 75% higher in those centres with a dedicated cancer genetics consultant. There was no significant difference in waiting times between high risk and "population risk" patients. The use of questionnaire-based referral "filtering" and the availability of a specialist cancer clinic did not appear to affect waiting times. Follow up rates depended on screening strategies.

In the same survey,[45] the Scottish centres interpreted referral criteria less restrictively and, partly because of this, had almost twice as many referrals and consultations per million of population as the rest of the UK. The Scottish centres reported that genetic testing was only available for research purposes (though this has since changed). A genetic test would only be discussed with 10% of the individuals at moderate risk or above, compared with 73% for the rest of the UK. There was no difference between centres in screening recommendations. The extent of relevant genetic risk information passed on to family members who may be at risk was not known and it was found that only 35% of women mentioned that one of the reasons for attending the clinic was to find out about the risk for other family members.

Overall, the survey concluded that Scotland was closer to meeting the structure

of their service model than the rest of the UK and that there were few family history clinics outside the regional genetics services.

The findings showed that the genetic services in Scotland have more attendees than in England and proportionally more patients at both moderate and at population-level risk, making the model more comprehensive but potentially more expensive than the one proposed by the Working Group report where population-level risk patients are (at least in theory) dealt with in the primary care setting and those at moderate risk in the Regional Cancer Unit.

A more recent study by Holloway and colleagues[76] evaluated a new mechanism for the delivery of cancer genetic services in South East Scotland by means of a trial which compared community-based service, provided by a genetic nurse specialist assessing patient's cancer risks in Primary Care premises, with a "conventional" joint genetics/breast surgeon clinic in a regional centre.

Patients and GPs expressed no clear preference for the type of clinic or service location (this means that there was no preference for either regional clinic, which was hospital based, or for a "community" clinic that was near the patient's home). Most of the "low risk" women assessed were less satisfied with the service received than higher risk patients, because the former would have liked to have access to other services (they wanted reassurance that they did not have cancer and they perceived mammography and regular clinical check ups as the means to achieve this).

Consultation time was greater in the community-based clinic, mainly because of the time taken by the nurse specialist to document the patient's family history but it could also be due to a more relaxed atmosphere between the patient and the nurse, with the result that the patient felt she could talk more openly to the nurse, than to a doctor ("reluctance to take the doctor's time").

In essence, establishment of a genetic cancer service within GP locality areas led to significantly increased rates of referrals but not measurable improvement in the patient's outcome.[47]

Fry and colleagues[77] showed that the novel community-based model of delivering breast cancer genetics services, described above, was comparable to the standard regional service when psychological outcomes were measured and that perceptions of women's risk for breast cancer were altered during the course of

the study (assessing both the community-based and the conventional regional services in South East Scotland).

Two separate studies in the UK[40,46] showed that there is a need for primary care to be involved in the selection process of patients at risk to enable appropriate referral to the specialist clinics. The GPs in South East Scotland, identified their role in the cancer genetics services as provision of appropriate referrals after taking a family history from patients and giving general information on screening, breast self-examination and emotional support. However, they felt that it was not their role to calculate the patient's cancer risk and admitted lack of confidence in delivering genetic advice. They asked for clear guidelines for referring patients.[40] Genetic nurse specialists can support GPs, providing counselling and follow up in "locality practice" clinics.

The Welsh genetics service has taken a particular interest in the cost-effective organisation of cancer family clinics. Brain and others[78] compared the psychological impact of providing specialist genetic input with surgical consultation alone, in women at high, moderate and low risk for breast cancer. There was a significant reduction in cancer risk perception and in worry among women at low or moderate risk under both management protocols. The high risk patients remained concerned about cancer and were less satisfied with their consultation but, again, there was no clear preference for the dual (genetics specialist plus breast surgeon) approach. This study, however, took "patient satisfaction" as the principal end point (rather that any longer term measure of clinical effectiveness) and it was acknowledged that the Welsh breast surgical team had unusual expertise in breast cancer genetics, unlikely to be shared by breast surgeons in all centres. In that study, molecular genetic testing for BRCA1 and 2 mutations was offered to women at "high" risk but for those with no living relative, it was not possible to offer genetic testing and it was not possible to examine the psychological impact separately for this group. There was a high level of satisfaction within the "low" risk category after receiving personal risk information, reducing the levels of anxiety and cancer related concerns. The conclusion was that the initial assessment of genetic risk could be performed by breast care specialists with limited experience in this specific area of genetics, reassuring women at "low risk" and selecting only the "high risk" women for referral to the specialist cancer genetics clinics.

Cancer genetics services in Wales operate a "Triage" system, whereby, on referral, a family history questionnaire is sent to all patients. If the questionnaire is not returned, the patients will not be seen at the specialist clinic.[79]

If the questionnaire is returned, a genetics counsellor contacts the patient by telephone and calculates her risk category, based on the information received. "High risk" patients are offered an appointment with the cancer genetic service. "Low risk" patients are counselled over the phone and returned to their GP. "Moderate risk" patients are invited to attend a breast clinic and will be managed according to the local protocol without further contact with a genetics specialist.[46]

In general terms, management of women at moderate or high genetic risk of breast cancer in virtually all UK centres means that, following their identification, they will be enrolled in a close surveillance programme involving regular follow-up with breast examinations and mammography where appropriate.

Prophylactic surgery will be offered in those cases where a patient has been found to be a carrier of a specific mutation predisposing to breast cancer. Specialists from other fields besides genetics will obviously have a role in the management of mutation carriers, for example in ovarian cancer screening and prophylactic surgery.

If a mutation carrier develops breast cancer, she will be at increased risk of a second primary carcinoma (in the same or contra-lateral breast). This is estimated at 2% or more per year, compared to an overall "second primary" risk of 0.5–1.0% per year in patients not selected on the basis of family history.[80]

Mutation-carrier cancer patients are also at increased risk of developing local recurrence after conservation treatment, particularly if the patient is under the age of 40.[81]

It is essential to maintain consistency and cohesion between the genetic services, cancer units and primary care across the regions and at present it seems more evident in Scotland than in the rest of the UK.[45]

2.3 Evaluation of breast cancer genetics services

Cost effectiveness of breast cancer genetics services currently available across the UK is being addressed at various levels but, as explained in Chapter 1, these services evolved in response to demand. Further data are therefore needed to evaluate them because the continuing increase in number of referrals is generating a workload stretching the capacity of the NHS, locally and nationally.[82–84] This demand for clinical service is likely to be sustained in view of high media interest in the discovery of breast cancer susceptibility genes and indeed in all matters relating to both breast cancer and genetics, leading to widespread public awareness of molecular genetic testing and possible prevention strategies.[65,85] For the commissioner of health services and, even in the UK, for health insurance companies, there is a need to identify what is relevant to this new evolving type of service as investment in those services may not have any evident return (financial or clinical) for years to come.[86,87]

In fact, full or even partial economic evaluations of the cancer genetics services are currently sparse, as demonstrated by a review by Griffith and colleagues,[87] in which it was recorded that cost effectiveness of screening young women is raised by focusing those services upon patients with a family history of cancer, rather than screening a wider segment of the population. Given the financial constraints within which the NHS must operate, direct costs and financial benefits are the primary components of cost-effectiveness calculations. Nevertheless, Griffiths and colleagues[87] recommended that economic evaluation of breast cancer genetics services in the future should take account of their *overall* impact upon the individual, her family and society. In this, they were reiterating the views of Hall and colleagues.[88]

Ideally, referrals should focus on individuals at *substantially* increased risk, for whom surveillance and genetic testing are justified. Appropriate resources should be allocated to achieve this, so that women's choices of intervention can be delivered. Health economic evaluation of the currently available breast cancer genetics services must also be based, at least in part, on consideration of the costs of care for women following a diagnosis of breast or ovarian cancer.[89]

Several interventions outlined in the flow diagram in Figure 1.1 and specified below, though provided through genetics services, are not routinely included

in some current measures of cost-effectiveness[90,91] and there is a need to examine in some detail current practice in the clinics for a realistic analysis of the cost-effectiveness of the services available in this country. I have concentrated on practice in Scotland, which, as explained in Chapter 1, differs from that in England and Wales. I believe this allows a more complete evaluation of the interventions that can be offered, their costs and benefits.

Interventions that have not been taken fully into account in the health economic evaluation of genetic services include costs of counselling, molecular testing for mutation carriers and prophylactic surgery (both mastectomy and salpingo-oophorectomy which are being carried out in increasing numbers of cases). Those interventions will need to be included in future analyses of cost-effectiveness of clinical practice in this field. Findings will become more robust when more uniform structured services are in place across the UK for screening or intervention.

Though currently there is only a limited literature in this area, Griffith et al.[92] recently presented the results of micro costing of NHS cancer genetic services in Wales (including counselling and genetic testing protocols). They found that the costs of providing such services are substantial, particularly in "high risk" cancer patients, (£2,510–£3,072 per patient). The overall mean cost per patient at any genetic risk of developing breast or ovarian cancer was between £675 and £2,909, with labour being the most expensive single element. Their conclusion endorsed my own view that there is a need for further analysis of different protocols, in terms of both costs and outcomes, in view of the wide variation in services, facilities and regional protocols in the UK.

Economic analyses are used to evaluate the intervention and assess the potential benefits of a given service (in other words, the value for money of a given healthcare intervention or technology) to make the most efficient use of limited resources. The principles of health economics, outlined in section 2.7, are applied to evaluate new methods of intervention. The outcome measures can be expressed in a number of ways, including the cost per life-year saved, number of adverse events reduced, the quality of life achieved and avoidance of healthcare costs incurred under alternative management protocols.

When compared to other government expenditures, costs in the area of healthcare are growing rapidly and this raises serious concerns.[93] The introduction of new technologies—not only related to pharmaceutical products but also in

new diagnostic facilities and new surgical interventions—increase unit costs but also allow healthcare professionals to intervene in a growing number of more complex diseases, the attendant benefits of which may not be fully assessable for many years. With advances in health technologies, there is a rise in the patients' (or consumers') expectations which increases the pressure on healthcare resources to make them available in a totally unrestricted way.[93]

With the increased demand for a given service, healthcare providers are under pressure to justify every single procedure and product used for the management of the disease. This certainly reflects the situation of genetics services in the UK. It is essential that complete and accurate records are kept of what happens to a patient attending the genetics clinic (and their relatives) to permit good audit of the given service. A comprehensive prospective database, recording data on pedigree structure, risk assessment, surveillance activity and interventions must underpin evidence-based recommendations for the future development of these services outcomes.[34,65,73] As there are increased pressures on NHS to provide economic justification for any developments in healthcare, this should be based on the best available evidence (mainly determined by research).

2.4 Management of breast cancer

Cancer therapy accounts for a substantial segment of healthcare costs in all developed countries. While general principles of treatment for breast cancer (to be discussed below) apply both to sporadic and familial cases, there are some special considerations relevant to the latter group.

If a breast cancer is detected early, for example by means of surveillance programmes, it is expected that the affected individual will have a better prognosis—meaning both lower treatment costs and a good prospect of cure or long-term survival.

The clinical management of breast cancer varies in relation to the extent of the disease. Early breast cancer diagnosis aims to obtain local control of the disease and to prolong both disease free survival and overall survival. When the disease is detected at more advanced stages, local control of the disease becomes difficult to obtain but, in some women, it is possible to prolong overall survival;

when the disease is found in sites other than the breast (metastatic) the aim of its management is palliation of the symptoms. Prolonging survival is not possible in most cases.[94] The majority of patients treated for operable breast cancer will have surgery, followed by radiotherapy and systemic adjuvant treatment. Only a small minority will be unsuitable for surgery by virtue of their poor general health or simply because they are elderly. Medical management of the disease in those few cases will be the only intervention.

When a tumour is large or locally advanced (with accompanying high risk of local or distant relapse of the disease) it is usual practice to treat the patient initially with systemic intervention (either endocrine therapy or chemotherapy). This is termed neo-adjuvant treatment (or primary treatment). It is intended to eliminate any possible metastatic cells that could be lodging in distant organs and also to facilitate subsequent surgery and radiotherapy to the breast. Further treatment will depend on the outcome of the initial interventions.

Palliative care for metastatic ("incurable") disease will involve either endocrine therapy or chemotherapy or both. Evaluation of the treatments available must address the impact on survival and on the patient's quality of life.

For both locally advanced and metastatic cancers, the interval between relapse and patient's death is very variable, from a few days to perhaps many years. On average, survival of a patient with metastatic cancer is 2 years from the time of the relapse diagnosis.

It is well documented in the literature that calculation of cost-effectiveness of measures taken to reduce the incidence of advanced malignancy is only possible if the recorded costs of treating those patients with advanced malignancy are full and accurate.[89] A study from Canada by Will et al.[95] revealed that the costs for treating breast cancer patients varied according to stage of the disease with cost varying from CDN $ 36,340 for stage IV to CDN $ 23,275 for early stage disease with in-patient costs for both treatment at diagnosis and terminal care accounting for 63% of the lifetime costs of care. They used the Statistics Canada's Population Health Model (POHEM) to estimate lifetime costs, discounted at 0, 3 and 5% rates.

Another Canadian study by Wai and colleagues[96] demonstrated similar results to the study by Will et al.[95] in that the costs of treating patients with incurable breast cancer are increased when patients are admitted to hospital (accounting

for over 50% of the costs in all age groups). The costs were highest in young women with metastatic cancer. The total mean cost to the health system in British Columbia, Canada, was CDN $ 36,474.33 per patient. Even higher costs have been reported from the USA in the same period.[97]

The (perhaps) surprisingly high cost of palliative or terminal care has a major bearing on calculations of cost-effectiveness of breast cancer family services, as discussed in more detail in Chapter 7.

These studies confirm the accepted belief that early diagnosis of breast cancer (with improved prospect of cure) is the key to reducing healthcare costs associated with the disease. Given that the cancer family clinics deal mainly with younger women, the potential for reduction in healthcare costs is great if surveillance programmes are effective. Kollias and colleagues,[98] in a study evaluating the use of screening for young women (aged less than 50 years) with a family history of breast cancer found that there was benefit from regular breast screening as it led to early detection of in situ carcinomas (pre-cancers) in this group of women.

Historically, breast cancer in younger women has tended to be detected at a relatively advanced stage and to behave aggressively.[99–101] Histological features of the tumours tend to confirm their aggressive nature and predict poor survival.

It may be, therefore, that family history clinic clientele, among whom the risk of early onset disease is increased, will require more intensive treatment of breast cancer when it occurs. That will potentially increase costs, both *ab initio* and because of the greater liability to unwanted side-effects of treatment. There are also likely to be complex effects on intra-family relationships and both of these factors will have implications for quality of life. Hence cost-effectiveness analysis in this setting is bound to be complex.

The diagnosis of breast cancer is made by "triple assessment" of a suspected lesion (this includes: clinical examination, breast imaging and histological diagnosis). Nowadays, it is common practice, to have a "one stop" clinic service for women with a breast problem to be investigated by a team of expert individuals. The patients with suspected cancers will be seen and appropriate measures will be taken for further management of the disease, while those with non-malignant conditions will be reassured of the benign nature of their condition. A "one stop" clinic will ideally offer same day investigations and results.

This is greatly valued by breast patients, particularly by the ones with cancer. It is hoped that this approach will prove cost-effective because it reduces the number of visits a patient will have to make to the specialised centre and because the patient will benefit both psychologically and in terms of eventual outcome from being fully and promptly assessed, with results available on the same day. However, the number of patients seen per consulting day is restricted by the time and resources needed to allow investigations and reporting to take place, with additional input from other specialities (i.e. radiologists and pathologists). In fact, it has been demonstrated that "one stop" clinics cost more per patient than a "conventional" breast clinic staffed mainly by breast surgeons and that the psychological benefits of a multidisciplinary "one-stop" service were seen only in the short term.[102]

A "one stop" clinic for patients with a positive family history of breast cancer will differ from the symptomatic clinic because the patient will usually be asymptomatic and will not have breast investigations other than clinical examination and mammography, hence limiting calls upon specialist pathology services. Follow up visits will follow the same pattern, using the same facilities in place for the very first clinic visit.

The principal objective of such clinics is detection of cancer at an early stage and, as indicated above, the economic rationale is that savings should result because, in general, treating disease at an early stage is less difficult and costs less than treating advanced disease.

Practice in the management of breast cancer is gradually evolving. Much recent press comment has concentrated on the introduction of new drugs and the question of how widely they may (or should) be available. As Dewar has illustrated, if treatment is changed, the costs of those changes depend not only on the cost of each individual procedure (or drug) but also on the numbers of patients involved.[103]

In the clinical management of breast cancer, these new cytotoxic drug regimes are now available and provide benefits for a proportion of patients making an impact on survival. The costs can vary but often are very expensive. Taxoid derivates are commonly used in advanced breast cancer but their use as adjuvant therapy is still under trial evaluation.

Recent advances in immunotherapy (e.g. Herceptin) also show potential be-

nefits and are likely to figure prominently in future management of the disease.[104,105] However, most breast cancers associated with BRCA1 mutations are negative for the HER-2 receptor and hence are unlikely to respond to Herceptin.[106] This illustrates another general issue of relevance to familial and sporadic breast cancer, that is the growing recognition of subtle, but important, biological differences within the spectrum of breast cancers. These will affect choice of therapy, prognosis and costs.

Some changes, however can be shown to reduce costs; potential savings can actually be realised when the disease is treated at an earlier stage, leading to early discharge from hospital (wherever possible).[107,108] One practical example of such a change in practice was a trial of nurse-led early discharge from hospital for patients who had undergone surgery for breast cancer.[108] There were no adverse effects on quality of life for those patients, little effect on carer burden and certainly improved communication between primary and secondary care. The practice could safely be implemented in a rural/urban area. This study concluded that the model of care with a nurse-led service was more cost-effective than the conventional service because in-patient care represents a very large component of surgical costs. The results from that study applied to 40% of the women with breast cancer who were offered enrolment and who were prepared to be discharged home earlier. However, sixty per cent of the patients declined to enter the study. In the main, these were older patients, more anxious and more likely to be living alone. This presents a dilemma for health care providers because the elderly population is increasing while at the same time there is an increasing pressure to reduce hospital stay. This study also demonstrated that, if the patient had a choice, she would prefer to stay in hospital until the surgical drains were removed.

These findings resonate with comparable studies in other aspects of cancer management, including those related to cancer family services. Randomised trials depend on patient participation which, in turn, is influenced by perceptions of benefit, which may not be rational but raise issues of autonomy and choice. It is clearly important, in gathering evidence on which to base changes in clinical practice to engage patients as fully as possible, even if this slows the rate of "progress".

It is becoming a requirement that treatment for a given condition has to be based

on evidence and enrolment into clinical trials at a large health maintenance organisation (HMO) did not lead to substantial increase in the direct cost of medical care nor undermine the quality of the treatment.[109]

Evaluation of costs of clinical trials should make due allowance for the investment in research infrastructure, data collection and other outgoings, including both direct and indirect costs of medical care considering that medical care outside clinical trials is likely to be more heterogeneous (in both cost and effectiveness) when compared to the "control arm" of a given clinical trial as Fireman and colleagues[109] have demonstrated.

2.5 Cost effectiveness issues

The economic assessment of medical interventions has become an integral part of decision making in health services with efficacy being the measurement of benefit achieved. The comparison of costs and consequences of a given intervention is part of economic evaluation methodology.

Evaluation is usually by means of structured clinical trials outcomes and effectiveness being measured as the decrease in disease morbidity and/or mortality achieved by the application of a particular intervention over a non-homogeneous population group.

Measuring cost-effectiveness of a practice involves the analysis of two or more interventions in relation to the health and economic consequences[93,110] as what the analysts term "health effects" such as "cases successfully treated" or "years of life gained". However, contemporary emphasis in disease management is not only on prolongation of life but also on its quality.

The Department of Health has provided guidance on how to assess the impact of policy making in health care (implications of a given policy in the identification, value and quantification of cost and benefits of the proposed measure).[111]

Data collected from economic studies are used to track vital information on costs, the coverage of health care, evaluation of access to care and, of course, the resources allocated. The fundamental purpose is to compare the value of a given intervention with the current "best" care provision, aiming to improve resource allocation and hence the efficiency of delivery of services involved.[110,112]

It is essential to identify efficient ways to make the best use of scarce resources in health care (establish the potential direct and indirect effects of health policies on the health of the population). This should be in form of development of frameworks aiming to identify such health effects. However, it must be recognised that different decision makers have different perspectives on costs and consequences. Subjectivity is a perennial problem, for example, in clinical trials where those administering the trial may have a different perspective on the benefits and disbenefits of a novel treatment from that held by the participating patients.[113] In general, forms of economic evaluation differ in the extent to which they can measure and value the consequences of intervention or therapy, but it is recommended that, in the presentation of the results, there should always be an incremental analysis included.[93]

Underlying the evaluation of all new developments (drugs, diagnostic and therapeutic technologies) in the NHS is the recognition that resources are scarce and difficult choices must be made. As a consequence, economic evaluation has become a much used tool in the NHS and pharmaceutical companies. Breast cancer screening is a classical example of a new technology whose economic evaluation has proved controversial (to say the least).

Before I present evidence on screening efficacy I think it is important to highlight some relevant information surrounding breast screening programmes.

2.6 Breast screening controversies

Screening of the general population seeks to reduce breast cancer mortality rate and there remain unreconciled arguments about screening outcomes. According to some critics, the actual benefit of breast screening programmes is overstated.[114] Several studies on mammographic screening for breast cancer report conflicting individual point estimates raising concerns about the quality of trials methodologies and the measured outcomes[115,116] and generating much debate amongst medical experts.[117]

The ongoing debates focus on whether screening for breast cancer in fact reduces disease mortality. Large scale clinical trials take a long time to get the answers to the questions posed at the beginning. As a result, studies may fail to generate a definitive answer because newer techniques become available while they

are still under way. Yet, it is necessary to have such large scale studies as only they can provide the detailed evidence-based information necessary to evaluate a given procedure or technique.

The breast screening programme in the UK was launched in 1980s and some screening units did not start until early 1990s. The target population was women from the age of 50 to 64 years. Beyond 64 years of age, if a woman wanted to continue to be screened she could do so but would have to make her own appointment with the local screening unit. Eligible women receive a letter of invitation for screening (every three years). General Practitioners provide the list of eligible women for screening to the Regional Screening Centre. Several units were invited to participate in research/audit projects within the screening programme looking at different issues (for example, the value of a screening programme for younger women typically from age 40 to 49 years; extension of the screening programme by inviting women aged 65 to 70 years; double reading of films; use of "two-view" films at the prevalent screening round).

Regardless of the precise arrangements made, the main aim of the programme was to reduce mortality from breast cancer by detecting it at an early stage. Forrest and Anderson,[118] reviewing breast cancer screening services in the UK and Australia, stated that the success or otherwise of screening will depend in part on tumour size and axillary node status as well as how aggressive the tumour is.

As in all screening programmes directed at a healthy population (which can be seen as doing some good from the public health point of view) the question arises "do the benefits really outweight the disbenefits, which may include discomfort, inconvenience, cost, increasing anxiety and even physical risks?" In the specific case of mammographic screening the most important negative aspects identified are anxiety, false reassurance, over diagnosis (and hence over treatment) and radiation-induced cancer. This last point has been addressed by Law,[119] who determined that, using modern imaging equipment, the benefits in terms of earlier diagnosis of cancer greatly outweigh the (miniscule) risk of cancer induction unless the woman is extremely young (under 30 years of age). Some authorities also suggested that compression of the breast by mammography can cause spread of an early localised cancer as well as any biopsy or operative intervention[120,121] in view of the disturbance of the dormant period

of cancer cells accelerating the spread of micrometastatic cells induced by angiogenesis but the "evidence" on which this claim is based continues to be debatable.

The incidence of breast cancer is increasing, and some of the apparent increase has been attributed to the rise of breast screening uptake. However, mortality from breast cancer has also fallen and this has been correlated both with earlier detection through screening and with improved treatment modalities. There has been a drive for better understanding of the process of screening, its risks and benefits, in order to improve the information and education provided for women invited to take in screening programme.[122–124]

In an interview given to Medscape Medical News, Professor Michael Baum stressed that when women attend for screening they should do so with full knowledge of its implications and based on informed consent. That implies weighing the benefits (lives saved) against the risks of false reassurance, unecessary surgical interventions and psychological stress.[125]

The UK National and other breast screening programmes appear to have delivered measurable benefits but some authorities are of the opinion that it is still too early to draw any conclusions about reduction in breast cancer mortality.[74,126]

Analysis of several randomised controlled trials on screening for breast cancer comparing outcomes of screened versus unscreened women demonstrated that there was a mortality reduction of nearly 30% in the screened population about seven to nine years from the start of the studies[127] leading to both professional and public increased demand for screening programmes. Nevertheless, it remains possible to argue that the absolute benefit of screening may be smaller than the associated risks.[128]

In a document reviewing recommendations on cancer screening in the European Union, prepared by the Advisory Committee on Cancer Prevention,[129] it is stated that "reduction in the disease specific mortality achieved in trials depends on the sensitivity, on the screening test, compliance, screening frequency, number of screens an individual has, follow up and benefit of early treatment. The negative aspects are dependant on the sensitivity and specificity of the screening test as well as possible side-effects of treatment". Indicators of performance of

a given screening method should be monitored regularly in order to maintain high quality screening.

Fletcher[128] has shown that the principal risks associated with mammography are directly related to false positive mammogram results, as further investigations are likely to be performed before an "all clear" is given to the woman. Levels of anxiety also relates to additional investigations. However, false positive mammograms do not diminish the attendance of women for further screening. It is important not to lower the "radiological threshold recall rate" in screening as that incurs the risk of cancers being missed. To achieve optimum balance between recall rate for suspicious findings and rate of missed cancers (i.e. between specificity and sensitivity) it is of paramount importance to maintain regular quality control checks of the process. The recommendation in America by the Agency for Health Care Policy and Research is that false positive (recall) rates should be no more than 10 % of all examinations.

Mammographic screening for women at significant risk for breast cancer targets a different age group from population screening because hereditary breast cancer tends to affect women at younger age. Until recently no substantive or co-ordinated method of screening for those women was available. Significant debate also arose about its potential efficacy, for several reasons. First, radiographic breast density is higher in young women, which means that small tumours may be more difficult to recognise. Second, breast tumours in this age group tend to be fast growing so that the opportunity for early diagnosis may be reduced. Third, these two factors could combine to increase both false positive and false negative rates of mammographic abnormalities and the belief amongst young women that they do not develop breast cancer at that age.[128]

Large-scale studies (discussed in detail later) have now generated adequate long-term data which show that screening young women with a significantly increased familial risk for breast cancer by regular mammography, with or without clinical examination is effective. However, with the recent introduction of MRI scanning of the breasts it became clear that this technology is more sensitive in the assessment of breast tissue that is mammographically dense and hence is particularly suited to screening young women. Several studies have suggested that women at high genetic risk will benefit most from having MRI scanning incorporated in their screening programme with both mammography and clinical

breast examination.

Recently, NICE guidelines[70] have recommended that surveillance programmes should be modified to take account of the new findings. Obviously there will be cost implications to this[70,130] and it is also the case that a substantial proportion of women cannot tolerate the claustrophobic experience of an MRI (magnetic resonance imaging) scan. MRI produces hundreds of images of the breast, cross-sectional in all three directions with use of contrast agent injection to enhance the breast tissue to be analysed. MRI uses a range of "markers" for cancer to allow the distiction between normal and abnormal breast parenchyma (these include tumour blood flow, size and appearances of the lesion). It does not use radiation, which is an important differentiation from mammograms (X-rays), a known factor causing DNA damage: in fact, it uses magnetic fields and radiowaves in the production of images.

Evidence from a Dutch study on the short term effects of screening women at significant risk for breast cancer revealed that women taking part in the screening programme had better quality of life in health-related matters when compared with the general population. That study also examined the effects of having a mammogram plus MRI in relation to anxiety levels. Relatively more women reported that mammography was more painful than MRI compared to the reverse (30.1% vs 12%) but the anxiety levels were high in 10.2% of women having MRI. This study showed that the impact of screening on the women sampled was generally favourable on both short-term generic health quality of life and general distress, perhaps reflecting the characteristics of women attending the screening programme (well, educated, healthy women who voluntarily entered the programme of surveillance).[131]

Several screening programmes have been fiercely criticised in view of their outcomes, particularly the screening programmes from Scandinavia as some results from meta-analyses have suggested that screening by mammography does not save lives and does not reduce the number of women having mastectomies even if cancer is detected early.[132,133] The report by Olsen and Gotzsche[132] also generated much debate in the scientific world, with the International Agency for Research on Cancer, the National Health Council of the Netherlands as well as the Global Summit on Mammographic Screening all concluding that the concerns and issues raised on the published analysis by Olsen and Gotzsche were mis-

interpretations of the facts and the data. Those institutions agreed that screening mammography could reduce the number of women dying from breast cancer.[117,134]

The Canadian screening programme which evaluated screening for breast cancer in women aged 40–49 years had also generated critics as the screened group unfortunately demonstrated more deaths than the control group. This was attributed to the poor quality of mammography and there were violations of basic rules in a randomised controlled trial as the trialists did not randomise entry into the study blindly.[117,135–138]

Data on both mammographic screening and MRI screening should continue to be collected and audited for long-term analysis of the efficacy of surveillance programme for high risk women and they should have both investigations on a yearly basis. With these combined, a measurable contribution to effectiveness of breast cancer detection and treatment in this cohort can be anticipated.

A reasonable conclusion from this debate may be that allocating limited resources for a proposed screening programme should be based on critical analysis of benefits, harm and costs of such intervention. On this basis, population screening of young women (under 50 years of age) for breast cancer is of dubious value. There is wide agreement that the key component of any screening programme in this group should be a short screening interval, which carries large cost implications.[139]

It is recognised that improvements in breast cancer treatment, stage of disease at presentation, new methods and techniques of breast screening as well as increased public awareness of the disease may all contribute to reduction in mortality. This will make it difficult to identify the specific effect of any screening programme in the reduction of deaths from breast cancer but it should be expected that the programme, combined with the other factors described, will result in further reduction in breast cancer mortality in the next 10 years.[140]

Women thought to be at high genetic risk for the disease should be screened at an earlier age and at more frequent intervals than is the case for a population-based screening programme.[48,51,98] International differences in the design of screening programmes are inevitable, given the differences in healthcare systems.[51] De Koning[126] showed that the estimated cost-effectiveness of screening ranges from 2,650 Euros per life-year gained in Navarra to 9,650 Euros in Germany. The

benefits of such programmes must be dependent on several factors: disease epidemiology, healthcare systems, quality of the screening programme, attendance levels and healthcare costs. However, definitive evidence on survival benefit is still awaited for this group of women.[98]

A uniform breast screening policy will not be possible in the foreseable future as there are so many differences between countries in the factors listed above, that contribute to cost-effectiveness.

2.7 Introduction to economic evaluation

For economic evaluation, a minimum of three elements are required in data collection: efficacy of the interventions concerned, costs of resources used and the impact of intervention on quality of life. However, reliance on these alone has limitations and it is likely that in the future, economic evaluation will use a wider combination of approaches, including the impact on families and on society as a whole, as mentioned by Drummond.[93]

In health care, the resource costs need to cover all aspects of organisation and implementation of a given programme, including any possible adverse events that may occur. Health service consequences relate to changes in health state, creation of new value in the programme and of course the resources saved, which can be calculated both for the individual and for the healthcare sector as a whole.

Improvement in health state relates to physical, emotional and social functioning of the individual. It may include reduced anxiety, increased mobility and thus increased leisure and work. It could thereby result in lower costs in the future and healthcare resources could then be freed up for use in other settings. However, in a healthcare programme it may not be possible to measure and price all relevant items for an overall economic evaluation of costs and consequences. It is important therefore to identify the most relevant cost drivers. Valuing costs gives an estimate of the worth of resources used by the programme.[141]

A measure that seeks to account for both changes in life expectancy and quality of life is called the Quality Adjusted Life Years (QALYs), gains in which permit the impact of treatment on a patient's disease to be adjusted for improvements or decrements in quality of life. This facilitates comparisons of cost-effectiveness

between given interventions but, as in the case of drug trials mentioned earlier, subjective evaluation of quality of life and indeed differences among patients themselves in what they regard as either acceptable or intolerable, mean that QALYs cannot provide an absolute standard but are, at best, an approach to that end.[55,142,143]

The effects of treatment on disease-related symptoms and the impact of side-effects can be measured by placing quality values on different life events, with utility indices ranging from 0 (death) to 1 (perfect health); multiplied by the time (years) spent in varying health states. The outcome of these calculations, expressed as additional QALYs gained, is widely used to define utility.

The number of QALYs will always be less than the survival time unless the patient maintains perfect health. Furthermore, as pointed out above, the assignment of QALYs to an individual patient is an inexact science. In large studies, however, averaging the QALYs gained (or lost) should tend to reduce subjective bias.

In cost-utility analysis it is normal to calculate medical savings related to the effectiveness of a given treatment. Those savings take account of the medical resources used in extending the life years, either by a novel treatment for that condition or by new forms of screening and detection of the disease, minus the resources used in treating a given disease without any new methods of screening and therapy (the "conventional" or "best alternative" care).

When it comes to calculating cost-utility, controversies have risen in relation to the inclusion or not of survivor costs—i.e. those healthcare costs which are avoided or curtailed because the treatment has cured or mitigated the disease. Those costs are not actually incurred but their absence is directly associated with the treatment, if indeed it is clinically effective.

Various health economists have had different views as to what should be included in the calculations and no consensus has been achieved.[55,141,144] Those in favour of including cost savings in the utility analysis maintain they should be part of an ICER (incremental cost effectiveness ratio). In other words, if the treatment is effective, the future medical costs that would arise in the absence of the new treatment are avoided.

Nyman described an alternative set of principles that can determine which costs should be considered for inclusion in the calculations of cost-utility. These prin-

ciples are based on standard welfare economics and would include treatment costs, downstream medical cost savings, travel costs, time receiving treatment (not forgetting informal care) and time in recuperation. All these should be included along with quality of life associated with the health status, when evaluating health costs.[55,144] Of course, from the perspective of the NHS, the most crucial elements are those costs directly incurred by the healthcare system and those savings that accrue directly to it, i.e. the impact on the NHS budget.

The simplest outcome of a given disease treatment that is effective is represented by the reduction in the probability of dying (or of an adverse health event leading indirectly to the individual's death) from the disease in question.

It is inherently difficult for a clinician to apply cost-effectiveness analysis to a group or cohort of patients since that requires the generalisation of findings to a large number of individuals, treating them as a uniform set, whereas in clinical practice management is invariably individualised. There is no "typical" breast cancer patient in reality, given the complex nature of the disease and treatment available. This was confirmed by Radice and colleagues[145] as the incidence and mortality rates for breast cancer vary immensely in different countries. However, even in clinical practice, some generalisations are both necessary and helpful. For example, management and hence treatment costs (both direct and indirect) are principally dependent on the stage of the disease at presentation.

Judgement on the effectiveness of an intervention for detection of early disease among individuals at risk must take account of the overall effect on the patient's quality of life, including the negative impact of the screening tests (which may include invasive procedures) with associated anxiety and discomfort, discussed above in Section 2.6.

An issue that arises frequently in the evaluation of cost-effectiveness of an intervention programme is "discounting". It expresses costs and outcomes that occur over a period of time, scaled to the costs at the starting date of the programme under evaluation, based on the economic idea that resources invested now will provide a return in future years and individuals have a time preference that favours health benefits in the present time rather than in the future.[146] Discounting is of particular relevance to the economic evaluation of breast screening because the natural course of breast cancer is highly variable with survival sometimes measured in decades rather than years, and recurrence is possible

even after twenty years of apparent cure. The range of treatments available has increased enormously over the past few years and so has the cost of drugs such as taxanes, trastuzumab (Herceptin) and other receptor kinase antagonists. That trend is likely to continue, so that costs of "salvage" therapy will grow even higher. This means that early detection and treatment, which might add several years of good quality of life but ultimately lead to late relapse, could incur very much larger costs than if the patient is diagnosed with advanced disease in the first instance and rapidly succumbs.

Furthermore, in relation to familial breast cancer services, the concept of discounting is highly relevant since healthy women have choices for regular surveillance over many years (with attendant anxiety surrounding each screening episode) or even for prophylactic surgery with the associated stress, risks and discomfort, to be set against possible long-term protection from the morbidity and mortality associated with late-presenting cancer. Yet, in many instances these women will never develop cancer at all, even if they decline to "take advantage" of the services offered by the cancer family clinic.

It has to be recognised that an unknown proportion of women at increased familial risk take the option of doing nothing at all about it—they discount long-term risks against peace of mind provided by current avoidance of the issue. It is, of course, almost impossible to obtain information about the psychological state of these women and hence to estimate whether, overall, they benefit or otherwise from non-use of cancer genetics resources.

Other conditions generate their own dilemmas regarding future (escalating) costs and how they should be taken into account in current cost-benefit analyses. For example, in childhood acute leukaemia, costly, but ultimately futile, treatment was standard practice for many years in the 1960s and 1970s with apparently little prospect of cure. However, nowadays over 70% of these patients are completely cured. Application of the discounting principle before cure was achieved would have generated quite misleading economic data.

The use of discounting in economic evaluation has therefore generated much debate.

Mansley and McKenna[147] reported how economic analysis can differ depending on the perspective taken by the decision maker. They identified several com-

ponents in the variation of perspectives, greatly affecting the perceived costs and benefits of cancer screening decisions.

Specifically, in relation to screening for breast cancer, the relative frequency of positive tests (with consequent follow-up diagnostic procedures and other interventions) contributes substantially to the outcome of cost-effectiveness analysis.

In addition to prevalence of the disease, other factors that also influence the analysis of cost-effectiveness are the unit cost of genetic testing and life-year benefits from the diagnostic interventions applied. A report by Brown and Kessler[146] points to the need for further economic studies in determining how both genetic testing and counselling can be delivered more cost-effectively.

Heimdal and colleagues[148] calculated costs for the familial breast cancer genetics services currently available in Norway, using the scale of charges levied by the Norwegian National Insurance Service (NIS). They found that genetic counselling and clinical follow-up interventions (clinical examinations and mammograms) accounted for a much greater share of total cost than laboratory procedures, a conclusion echoed more recently by Griffith et al.[92] The Norwegian group estimated that the cost per life year gained was Euro 753 and that to identify high risk families through genetic tests of all incident breast and ovarian cancers for Norwegian "founder" mutations in BRCA1 (see below) would increase that figure to Euro 832.

The study by Heimdal and colleagues[148] (discussed further in Chapter 7) also assumed that if BRCA2 mutation-related cancer treatment has a better prognosis than BRCA1 associated tumours, then molecular genetic testing for BRCA2 mutations could be very cost-effective because the outcome would be substantially improved by early detection.

Genetic testing is defined as analysis of human DNA, RNA chromosomes proteins and other metabolites in order to detect inherited disease-related mutations. For clinical purposes, identifying carriers of such mutations improves the accuracy of risk assessment and can contribute to establishing clinical diagnosis or prognosis but devising effective interventions to prevent manifestations of the disease has proved difficult for both scientists and clinicians.[149]

The costs of molecular genetic testing will vary, depending on how commonly specific mutations occur in the population examined (i.e. how easy it is, technic-

ally, to undertake efficient laboratory screening). The variety of genes and mutations implicated in many diseases can limit the predictive power of such tests. Familial breast cancer is a case in point, as illustrated from Table 1.3. Given the technical complexity of the work, special quality assurance is expected from the laboratories performing genetic tests and contributes to the diagnostic costs.

In Norway, five relatively frequent "founder" mutations have been recognised, some specific to certain regions of the country. "Population" screening, as contemplated in the paper by Heimdal may therefore be economically justifiable. Families at high risk, identified through this approach will be given priority access to the resources of the "high risk" breast cancer genetics service.

In the absence of common "founder" mutations, mutation screening of both genes (BRCA1 and BRCA2) is expensive (estimated at Euro 2,250 per sample). There is some hope that when the process becomes automated, it will become much cheaper to run these tests.

It is important to highlight the economically relevant point that several tests used in screening high risk family members for cancer (notably mammography) are generally performed several times; at least annually, over a prolonged period, typically 15 years, while genetic testing for an individual at increased risk for a given disease or condition is likely to occur only once.

In a recent study, Sevilla and colleagues[150] raised concerns about the holding of gene patents by a privately owned company. This could influence the decision making process within healthcare systems, regarding identification and adoption of the most efficient strategies for genetic testing (due to the monopoly of such a company in exploiting techniques for direct sequencing of the genes). They demonstrated that other laboratory technical strategies could be used with similar effectiveness, reducing the costs of the tests. The average cost per mutation detected, when the mutation test was undertaken by the patent-holding company, at 9,882.5 Euros, was the highest of all the alternatives considered. This also highlights the general point that calculations of cost/benefit ratios must be influenced, to a degree, by the different ways in which health care is financed in different societies. This adds to the difficulty of combining the limited data available from a range of sources, countries and healthcare systems.

An analysis of effectiveness and costs of a genetic counselling and mammographic screening programme in high risk breast cancer families was performed

by a group in Barcelona.[151] They estimated that the annual cost of screening mutation carriers is 86.83 Euros until breast cancer is diagnosed. There was a measurable cost benefit to the overall programme when mutations were detected because non-carriers of mutations could be identified and excluded from further clinical surveillance. When breast cancer was identified, the patient would be referred to the appropriate specialist department for treatment and, though numbers were insufficient for definitive conclusions, there appeared to be a trend towards lower cancer stage at diagnosis if the patient had been enrolled in the screening programme (as also demonstrated in a study by Kollias et al. in 1998[98]).

Balmana and colleagues' study in 2004[151] made use of a decision tree estimating the survival benefit and cost-effectiveness of their clinical genetic counselling / screening programme. They provided both genetic counselling and genetic testing, which entailed a cost of 338.15 Euros/person in the first year of inclusion of a given family in their programme. The study found that the cost effectiveness ratio of their programme was 4,294 Euros per life-year gained and they concluded that such programmes may be cost-effective. Unfortunately, this group did not include the costs of treating the patients diagnosed, nor the cost savings achieved through earlier diagnosis, nor the potential damage from a false positive result, all of which might have changed the cost-effectiveness ratio. They also excluded from the analysis other interventions such as chemoprevention and prophylactic surgery, due to the low numbers of relevant cases in their study.

It is a reasonable prediction that young women presenting with late stage (essentially incurable) disease will require long term treatment and nursing care and hence will be unable to contribute to the overall economy. In the absence of preventive intervention or early detection, therefore, costs to the community will inevitably be higher. As discussed in relation to "discounting", one may even argue that diagnosing breast cancer at an advanced stage can lead to a shorter period of morbidity (because of the patient's earlier death from the disease) than if a woman is treated for early breast cancer.

In general, existing data on the cost effectiveness of current services for familial breast cancer are inadequate. Recommendations based on unproven assumptions are suspect and more firm evidence is required. Experimental approaches should be supported, even if this means that, in the short term, some medical

interventions have to be allocated more resources than would be justified if their effectiveness were already known.[152]

2.8 The role of prophylactic surgery

The economic impact of prophylactic intervention was not discussed in the Norwegian study as data were not then available.[148] Subsequently, however, several important studies have been published.

From a retrospective series, Hartmann et al.[153,154] demonstrated a reduction in the risk of breast cancer, of at least 90%, if women at increased risk had undergone prophylactic mastectomy. The residual risk depends on the amount of breast tissue remaining after surgery. Total bilateral mastectomy is the procedure of choice.

It is important to highlight that, regardless of the procedure chosen by the patient, the surgeon should remove as much breast tissue as possible to have the risk reduction maximised. The recently published PROSE study[155] showed that the two women diagnosed with breast cancer after undergoing prophylactic surgery (2/105 or 1.9%) had had what is technically termed "subcutaneous mastectomy". This is not optimal as a prophylactic procedure since it leaves substantial residual breast tissue intact, including the nipple-areolar complex. This will play a part in contributing to residual risk. However, 184 patients of 378 (48.7%) in the matched control group who did not have any prophylactic intervention developed breast cancer. There is therefore no doubt that prophylactic surgery vastly reduces the risk for breast cancer in BRCA1/2 mutation carriers.[155]

Skin sparing mastectomy and breast reconstruction are now offered to virtually all women comtemplating risk reducing surgery but this can complicate future mammographic or clinical screening. In the Manchester series of prophylactic mastectomy,[156] 8–10% of the women attending the clinic with a lifetime risk of 1 in 4 or above have sought advice on risk reducing surgery; 6% have proceeded to surgery. This figure rose to 11% in women at 40% lifetime risk.

A second study from Manchester, recently reported,[157] specified that patients attending the regional family history clinic for regular screening were given information on risks for contra-lateral breast cancer when cancer was diagnosed.

The issue of undergoing bilateral mastectomy and breast reconstruction at the time of the (unilateral) diagnosis was also discussed with the patient and the uptake was compared with that of women with breast cancer (and identified as carrying a BRCA1/2 mutation) from other surgical clinics. They identified 70 such women. Sixty-five percent of the Manchester BRCA1/2 mutation carriers and 59% of the ones at high risk for the disease (but without known mutation) opted for contra-lateral mastectomy, while only 10% of the women identified as mutation carriers from other clinics opted for such intervention (9/88). Data have been gathered prospectively to assess whether salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers could decrease risk of both breast and BRCA-related gynaecological cancers.[158] In that study, of 170 women who met the entry criteria, 98 elected to undergo salpingo-oophorectomy and 72 underwent regular surveillance for ovarian cancer. Breast or BRCA-related gynaecological cancer was diagnosed in 4 women in the salpingo-oophorectomy group compared to 12 women in the surveillance group demonstrating that the risk of breast or BRCA-related gynaecological cancer was significantly lower in the salpingo-oophorectomy group.

The recent findings of the PROSE study[155] indicated that women with BRCA1 or BRCA2 mutations who undergo bilateral prophylactic mastectomy have their risk for breast cancer reduced by 95% if they also have a previous or concurrent prophylactic salpingo-oophorectomy.

In women who have kept their ovaries intact, the risk is reduced by 90%. Such results provide strong evidence for inclusion of prophylactic salpingo-oophorectomy in the discussion of risk-reduction management for women at risk of hereditary breast or gynaecological cancers.[158] A comparable study[159] also found that prophylactic oophorectomy in premenopausal carriers of BRCA1/2 mutations led to a reduction in breast cancer risk of around 50%, with a follow-up period of eight years and hence support the recommendation to perform prophylactic oophorectomy in mutation carriers of BRCA1 or BRCA2 soon after childbearing is completed. Surveillance alone for those women did not show a reduction in the proportion of advanced ovarian cancers diagnosed nor any effect on ovarian cancer mortality (estimated to be 80% at 5 years for stage III disease). In this and other reports, a number of patients with germline mutations in BRCA1 or BRCA2 genes have been found at prophylactic oophorectomy to have

coincidental early ovarian tumours which were not detected by currently available screening tools, namely level of glycoprotein CA-125 marker in the plasma and transvaginal ultrasound.[48,61,160]

Current evidence thus indicates that the screening tools for families at increased risk for ovarian carcinoma are not reliable in detecting cancer at an early stage according to FIGO (International Federation of Gynaecology and Obstetrics) criteria.[61] It is also important to highlight that when prophylactic oophorectomy is planned it should include the removal of the fallopian tubes because of the potential risk (although rare) of a serous papillary cancer arising from the intramural portion and fimbriated end of the tube.

According to a Canadian study, 16% of all fallopian tube malignancies are caused by germline mutations in BRCA1 or BRCA2 genes and should be considered part of the hereditary breast-ovarian cancer syndrome.[161,162]

Several other reports support the conclusions of the Canadian study. The present recommendation is that women at risk for ovarian cancer should also have the risk of fallopian tube carcinoma discussed when prophylactic risk reducing oophorectomy is to be performed and as a result, this should always include removal of the fallopian tubes.[163,164] Paley and colleagues even recommended that those patients should also consider having a hysterectomy performed at the time of oophorectomy, in view of the growing number of primary tubal carcinomas in mutation carriers and given the biological parallels between ovarian and both primary peritoneal and tubal carcinomas.[163]

Even after salpingo-oophorectomy, there remains a small and currently irreducible risk of primary peritoneal cancer of ovarian type.[165,166] The best estimate of this lifetime risk is around 1–2%.[158,159,167]

Given that ovarian cancer risk is very significantly reduced in BRCA1/2 mutation carriers after prophylactic oophorectomy and that the risk for breast cancer is substantially reduced by this procedure if the patient is premenopausal. There remains some debate and uncertainty as to the use of hormone replacement therapy (HRT) in those women.[159,168]

A recent epidemiological study by Armstrong and colleagues demonstrated that prophylactic oophorectomy extended life expectancy in women with BRCA1/2 mutations irrespective of the use or not of HRT post-oophorectomy and that the

decision on the use of HRT after prophylactic surgery should be based on the patient's quality of life rather than life expectancy. HRT should be discontinued at the time of expected natural menopause (that usually is around age 50 years) for most women.[169]

The options of surgical management should be fully discussed with the patient as the decision to undergo such procedure is complex and could incur long term psychological distress.[170] All risk reduction interventions for breast and/or ovarian cancer are not free of potential complications, which should be discussed fully with the individual seeking risk- reducing interventions before giving informed consent for the procedure.

Surgical complications have been more frequent in women who had both prophylactic mastectomy and immediate breast reconstruction. Women who underwent prophylactic mastectomy only, experienced fewer complications (presumably due to the less extensive nature of the procedure). Unfortunately it is not possible to predict whether a given patient will develop complications or not. However, it is possible to take measures prior to each form of intervention to keep complications to a minimum.[171]

With regard to prophylactic oophorectomy, complications are fortunately rare. For chemoprevention regimes, complications (side-effects) are generally understood and are characteristic of each type of medication. Of course, the main worry for prophylactic surgical interventions is the potential risk of breast and/or ovarian cancer happening after the surgical procedure has been performed.[165,172] This will be discussed later in the thesis.

2.9 Prophylactic surgery versus regular surveillance

Screening young women for breast cancer is controversial; there is no consensus on cost-effectiveness of population-wide screening for women under the age of 50 years. Selecting women who demonstrate a significantly increased risk for the disease should be more efficient.[173]

The influential Schrag reports[90,91] on decision analysis to determine the relative merits of surveillance versus prophylactic mastectomy and oophorectomy in young women with BRCA1 or BRCA2 mutations, predicted substantial gains

in life expectancy for prophylactic mastectomy (range: 25–97% risk reduction) patients but smaller gains from prophylactic oophorectomy (range: 25–75% risk reduction). The gains noted in mutation carriers ranged from 2.9 to 5.3 years of life expectancy from mastectomies and from 0.3 to 1.7 years of life expectancy from oophorectomies. Neither approach gave complete protection against cancer.

According to Schrag's model, if a BRCA mutation-carrying woman diagnosed with breast cancer has prophylactic surgery on the opposite breast at the time of her treatment, this will achieve most benefit in terms of life expectancy. When a mutation is detected some years after initial treatment for breast cancer, the patient may wish to consider prophylactic surgery and it has been calculated that she will still have survival benefit, provided there is no recurrence of the original tumour either locally or in distant organs.

Not surprisingly, patients with sporadic (i.e. non-genetic) breast cancer gain less from prophylactic surgery because their risk of a second primary tumour is lower. The procedure is not currently recommended for them.

If mutation status is uncertain, in order to maximise the survival benefit from available interventions, a cautious assessment should be made of the "historical" genetic penetrance levels which reflect the cumulative risk of developing cancer within the individual patient's own family. Those at risk within high penetrance mutation families will have 85% cumulative incidence of breast cancer and 40% of ovarian cancer. Those figures, used by Schrag and colleagues, were based on Breast Cancer Linkage Consortium results.

A collaborative study (to which I contributed with Tayside data) reported by Møller et al.,[48] on the outcome of breast cancer diagnosed among women enrolled in special surveillance programmes provided data on 249 patients from 5 different countries, analysed by tumour characteristics, BRCA mutation status and oophorectomy. They found that overall survival at 5 years was 89%, with relapse-free survival being 87%. Mutations were unevenly distributed: 36 patients had BRCA1 mutations and 8 had BRCA2 mutations. Because numbers were so low, the latter were excluded from subsequent comparison between BRCA1 mutation-positive patients and non-mutation carriers. For both node-negative and node-positive patients grouped together, 5-year survival was more favourable for those not carrying the mutations (91% vs 63%) and, even among

node-negative patients, 5-year disease-free survival was more favourable in non-mutation carriers (96%) when compared to mutation carriers (75%). In BRCA1 mutation-positive patients who had undergone bilateral oophorectomy at the time of breast cancer diagnosis, a much more favourable disease-free survival was noted.[48]

In summary, BRCA1 mutation carriers have worse survival when cases were compared to the total of the remaining group but mutation carriers appear to benefit from undergoing bilateral oophorectomy. These findings are in keeping with other reports of adverse prognosis among BRCA1 mutation-carriers (reviewed[174,175]) and demonstrate that it is essential to collect data prospectively to permit thorough evaluation of management options in distinct subgroups of breast cancer families.[48] A more complete discussion of this topic, with recent data both from my own experience in Tayside and from the European collaboration, is the main theme of Chapter 5.

In a recent study, Anderson and colleagues[1] concluded that the most cost-effective strategies for prevention of both breast and ovarian cancers in BRCA mutation carriers were oophorectomy alone and oophorectomy with mastectomy. Those strategies were both better than surveillance alone. They also deduced that the survival benefit of those women who have had their surgery by the age of 30 years was 4.9 years and that there was an increment in the survival benefit to 7.8 years if the penetrance function of the mutations was raised. Unfortunately the study was based on the application of a Markov model with hypothetical data and may not reflect what happens in real life. Those issues will be discussed later in the thesis.

2.10 Conclusion: current views on cost effectiveness of breast cancer family history clinical services

Screening programmes for inherited breast and ovarian cancer high risk women involve several stages: the assessment of the individual's risk for the condition and subsequently genetic testing for the ones at high genetic risk for the disease plus other interventions that are available to them for consideration. It is important to recognise that the calculations in Schrag's reports[90,91] have been based on

theoretical predictions and rely on unproven assumptions about the efficacy of screening and of prophylactic surgery for both breast and ovarian cancer risks. The Møller (2002) study[48] is the first substantial report of actual data relevant to these questions, drawn from a prospective series.

Some specific flaws in modelling for the Schrag predictions have since been identified. Women at increased genetic risk of breast cancer have been treated as a homogeneous group, whereas, in fact, only a minority of women with a positive family history are from BRCA1/BRCA2 families.[18,176] Screening is not uniformly effective for all subgroups of women with a positive family history of the disease.

Even when BRCA1 positive tumours are detected early (i.e. small, node negative tumours), recurrence rate is high (much greater than the 20–38% assumed by Schrag).[48] The Schrag reports do not recognise the effect of oophorectomy or recurrence rate on BRCA1 positive breast cancers.[158,159,167,177]

Improvement in performance of clinical genetic services depends on the development of clinical guidelines for both breast and ovarian cancer surveillance screening. There are several strategies that are currently used to improve specific services in clinical practice varying from policy-level strategy, practice-level strategy and motivation strategies. As a result, some studies demonstrated that there is a need to implement multiple strategies for a more efficacious service.[178] Accurate risk assessment (i.e. correct targeting of resources) is probably the most important tool for maximising efficiency of breast cancer family services. Further development of Cancer Genetics Services and allocation of resources to them should clearly be based on accumulation of real evidence and the present study is intended to contribute to that end. The issues reviewed herein are discussed in more detail in later chapters, and in the light of more recent (unpublished) findings to which I have contributed.

In conclusion, the following key questions are addressed in order to meet the aims and, objectives of this study:

1. Is it possible to "screen out" referrals to the breast cancer family clinic of women whose risk is below the "moderate" level at which regular special surveillance is considered appropriate?

2. Can this be done accurately and cost-effectively and without detriment to those below the "threshold" level of risk?

3. Are current settings for the "threshold" valid?

4. What are the appropriate roles in the selection processes for the families themselves, primary care staff, personnel in the specialist genetics centre and central data sources (Cancer Registry and Registrar Generals' records)?

5. What are the outcomes of surveillance programmes for women at increased genetic risk of breast/ovarian cancer?

6. What are the true costs of these programmes and what savings can be achieved by early detection of cancers?

7. How do the estimates compare with costs and benefits of prophylactic surgery?

8. What further studies are required to improve the quality of evidence?

Finally, by addressing these questions, can specific evidence-based recommendations be made for cost-effective management of distinct categories of familial breast cancer risk?

Chapter 3

Material and Methods

3.1 Basis of the linked studies and funding

The author has worked personally in the Tayside Breast Cancer Family History Clinic since 1995, collaborating in close partnership with colleagues within the BIOMED 2 Demonstration Programme (European Community BIOMED 2 Project: "Familial Breast and Ovarian Cancer: Audit of a New Development in Medical Practice in European Countries") from 1996 to 1999. Relevant outcome data from that programme are included in this thesis.

An "analytical framework" with current pathways of patient management since referral to the Tayside breast cancer family history clinic was constructed, following the model adopted by the US Preventive Services Task Force.[179] It identifies the key questions that should determine each element of the patient's journey, including decisions about genetic testing, prophylactic surgery and breast cancer treatment of women that have been under regular surveillance through the clinic (Figure 1.1).

Following this analytical model, I have set out to address at least some of the key questions and to adduce evidence upon which to base a modified clinic model for the Tayside cancer genetic services, with implications for comparable programmes in other centres. The aim is to optimise clinical practice and resource allocation in this emerging field of health care.

A grant from the Chief Scientist Office (Health Services Research Committee), Scottish Executive Health Department for the project "Evaluating a New Model

for Cancer Genetics Services: Co-operation between Primary care, Nurse Specialist and Hospital Clinic" was awarded in 1999 to the Tayside Breast Cancer Genetics Group.

The author was one of the co-holders of that grant, with particular responsibility for clinical examination of patients, collation of data on cancers arising in women under surveillance and health economic aspects of the study.

A major element of that study was evaluation of the process of risk assessment, carried out in the genetics department and making use of: a) Family history form completed by each family, b) Access to NHS clinical records and cancer registry and c) Access to Registrar General's records of births, marriages and deaths. All this could be done without requiring the referred family member to attend the clinic in person.

One important question was whether it was acceptable (and "safe") to carry out this evaluation and communicate reassurance (for those at "low" risk) by post or whether one face-to-face interview would be required. Suitable patients were therefore randomised to "postal" or "interview" contact, the interviews being conducted by a genetics nurse specialist or a genetics associate.

The duration of the period of evaluation of the new model was thirty months and a triage protocol for the delivery of the cancer genetics services was used. This study is referred to, for convenience, as the "Triage" project and is the subject of Chapter 4.

The other grant-holders were: Professor Michael Steel, Professor Frank Sullivan, Dr David Goudie, Professor Alastair Thompson, Professor Mo Malek (who sadly died in 2001) and Dr Manouche Tavakoli (who took over supervision of the health economics aspect of the study). The grant was activated in February 2000 with the appointment of Dr Dorothy Young as a Genetics Associate.

Within the terms of the grant there was a particular interest from the Chief Scientist to have an evaluation of the economic implications of the new model. Money for a full time PhD student was allocated in the research grant for this specific purpose.

I was invited to undertake the economic evaluation and efficacy analysis on a part time basis. Two sessions per week from my current work were allocated specifically for the study. As I do not have formal training in economics or man-

agement, I attended classes at the Department of Management and Economics at the University of St. Andrews to gain greater understanding of the process required for the analysis.

The study protocol was submitted to the Local Research Ethics Committee for consideration and approval was granted. From February 2000 to August 2002, all women referred to the Tayside breast cancer genetics clinic were invited to participate in a randomised trial comparing the provision of information about their risk for breast and/or ovarian cancer by letter or by a personal interview.

It is important to highlight that this would only apply to women thought to be below the "threshold" level of risk for breast cancer (as defined by SIGN guidelines) and hence not eligible for inclusion in a programme of regular clinical and mammographic surveillance.

In addition to the above specifically funded research projects, in order to address the issues listed at the end of Chapter 2, I have gathered material from observation of clinic operation over ten years and have participated in several exercises in data analysis, usually starting with the Tayside clinic and then, if there appeared to be interesting findings, extending studies to include the other Scottish centres and, in some instances, other centres throughout Europe.

3.2 Study setting and patients

The Tayside Breast Cancer Family History Clinic provided the " base" for the studies recorded in this thesis. From 1994 onwards, the operation of the " Breast Cancer Family Service" was discussed with local General Practitioners and other interested healthcare professionals (community nurses, staff of "well woman" centres etc) at study days and through articles in the "Tayren" ("Tayside Primary Care Research Network") Newsletter and on the website of the Dundee University Department of Surgery and Molecular Oncology.

Referrals to the service were received from both primary care and other breast units. The relative proportions coming from these two routes have changed during the ten years of my involvement, as recorded later.

All referrals were forwarded to the Genetics Department at Ninewells Hospital and, before any clinic appointment was offered, each woman referred was con-

tacted by letter with a request to complete (as far as possible) and return a standardised form (see appendix) detailing family structure and reporting any instances of cancer among relatives, with as much information about these illnesses as the family could provide.

With this information on the patient's family history, risk assessment could proceed, though that often involved checking the information by gaining access to the case notes of affected relatives (with appropriate informed consent) and interrogating the Scottish Cancer Registry and/or Scottish Registrar General's records of births, marriages and deaths.[180] These further steps enabled validation of information and extension of the family history as presented by the referred woman.

On completion of these steps, a consensus decision was taken by the specialist staff at the genetic department on the probable level of genetic risk, assigning each referred women to "High", "Moderate" or "Low" ("Below threshold") category, according to SIGN guidelines. In principle, management should then have followed the protocols outlined in Table 3.1.

However, prior to the Triage study, we were concerned that if "low risk" women were not seen in person, important information might be missed, leading to errors in assignment of risk category. One purpose of the Triage study was to evaluate these concerns.

An additional problem was the rather frequent failure of referred patients to return completed "Family History" forms–some 25% failed to do so even after a reminder letter. Many brought the completed forms with them when they attended the multi-disciplinary clinic but this did not fully achieve their purpose, which was to provide the geneticists, in advance of the appointment, with complete information on which to base their risk assessment and counselling. Therefore, from 1995 until 2000, all women referred to the service were seen at least once at the multi-disciplinary clinic.

Those at "low" genetic risk were then discharged, but advised to remain "breast aware" (i.e. to notify any breast symptoms to their GP), to inform the genetics clinic of any new breast or ovarian cancers among close relatives and to join the National Breast Screening Programme (NBSP) at age 50 years. All had a clinical breast examination carried out by myself and many also had a "one-off" mammogram prior to discharge.

Those at "Moderate" or "High" risk were enrolled in a programme of annual return visits, starting from age 35 years or five years younger than the earliest age of onset of breast cancer in a relative.

Clinical examination and mammography were carried out at every visit for most of these, with the exception of some "Moderate" risk women whose affected relatives had all been over 50 years at diagnosis, when mammography was undertaken only every second year up to age 40 years and annually thereafter. At each return visit, women were asked specifically about any new cases of breast or ovarian cancer among relatives.

Personal information about all the women referred was recorded to enable analysis of all sources by age, social class, initial genetic risk category, genetic risk category after checking of family history forms, extent of search (to establish risk status), final genetic risk assessment.

The Tayside clinic was privileged to have NBSP personnel and equipment, ensuring optimal quality. Mammography was not offered routinely to women younger than 35 years of age or if it had been performed within the last 12 months unless the woman was thought, on clinical examination, to have an abnormality requiring further investigation.

For women who had a relative with onset before age 40 years, mammography was generally performed at first consultation as a baseline and thereafter as per protocol.

Regular annual surveillance continued until age 50 years, when all women became eligible for participation in the NBSP which provides high quality mammography at three year intervals and were subsequently discharged from the clinic, provided no new cancers have occurred in their relatives and that they themselves were free from any breast abnormality at their last surveillance appointment before discharge. However, NBSP represents a substantial reduction in intensity of surveillance compared to the Breast Cancer Family Service (annual) protocol.

For women judged to be at "High" genetic risk, therefore, surveillance was continued beyond age 50 years, but at eighteen month intervals rather than annually. The same service was offered to those women in the "Moderate" risk category who had two or more affected relatives diagnosed after age 50 years.

In most cases (unless a BRCA1 or BRCA2 mutation had been identified) these women were discharged to the NBSP by the age of 60.

Counselling was given by a genetics associate, genetics nurse specialist or one of two consultant geneticists, while the surveillance of those women thought to be at increased risk of breast cancer (i.e. above guidelines threshold) was performed by a specialist breast surgeon (normally myself). Radiographers obtained breast imaging and the films were read by a radiologist with breast screening expertise.

Investigations, such as further breast imaging by ultrasound, and biopsy procedures were carried out during clinic appointments when required. Referrals for ovarian and/or other cancer screening were discussed with the patient; further counselling appointments were made for those at high risk and/or known to have a mutation in the family, in preparation for molecular gene testing.

For "High risk" women, identification of a living affected relative was needed in order to obtain informed consent for DNA testing (current protocol requires the affected living relative to be tested first).

Once consent was obtained, DNA testing was performed and any result was reported to the affected relative tested. If this confirmed the presence of a pathogenic mutation in BRCA1 or BRCA2, then counselling in respect of specific testing was offered to the unaffected relative who had originally been referred.

Other "at risk" relatives were also offered information about the family mutation and enrolment in the surveillance programme if this had not already been arranged.

Information on prophylactic surgery was given to patients with a proven positive genetic test for mutation in BRCA1 or 2. Women at high risk for the disease but who did not have any living relative to allow genetic testing to take place also had the opportunity to discuss prophylactic risk-reducing surgical interventions.

The breast surgeon would discuss prophylactic breast surgery with the patient and referral to the Plastic Surgery Department was made for those wishing to consider breast reconstruction. When women decided on having both prophylactic mastectomy and immediate reconstruction, this was performed by a breast surgeon and plastic surgeon together.

An appointment with the plastic surgeons was always offered to patients having prophylactic risk reducing breast surgery (i.e. prophylactic mastectomy) giving them the opportunity to discuss options of breast reconstruction and whether they would prefer to have it performed at the same time or as a delayed procedure. The plastic surgeons would also arrange for the patient to be seen by one of their plastic surgery nurse specialists to discuss further the technicalities of reconstruction options given to them and to show the patient a portfolio of case photographs of breast reconstruction.

Detailed information on prophylactic oophorectomy (whenever appropriate) was given by the gynaecologist at a separate consultation with the patient. Ovarian screening issues were also discussed with women seeking advice on the subject. They were given information on the pros and cons of having ovarian screening, based on the most recent data available. Unfortunately, these did not show any benefit from such intervention.[61]

With the increase in the numbers of patients on regular surveillance at the clinic, it became evident that there was an urgent need for further staffing to share the load of clinical breast examination under the direction of myself. Therefore a research nurse working in the IBIS I chemoprevention trial[181] was trained to assist me as well as enrolling patients for the chemoprevention study.

With this help, we were able to ensure that the scheduled timetable for regular repeat surveillance was met. This was important in view of the evidence from the EC Demonstration Programme that delays or "slippage" in the planned follow up of women at risk leads to an increase in the number of "interval" cancers (i.e. those presenting clinically between screening rounds) and hence to loss of opportunities for diagnosis at the earliest possible stage.[182]

During and after the Triage study (i.e. from February 2000), the protocol shown in Table 3.1 was followed more stringently, though women who had not returned a completed family history form were still being seen at the multi-disciplinary clinic while effective ways of dealing with this problem, without discriminating against women who have genuine difficulty in complying, are worked out with local general practitioners. The Triage study is the subject of Chapter 4.

From the summary outlined below, the numbers relate to the distribution of referrals for recruitment in the "triage" study.

Table 3.1: Management protocol followed by the Tayside Breast cancer family service. If malignancy was detected in any risk category, treatment would be arranged as per local protocol.

LOW RISK	Reassurance letter explaining why patient was at low risk (patient and their GP) One to one consultation with genetics associate to explain the risk assessment. Clinical breast examination before discharge. Advised to be "breast aware" and enter National Breast Screening Programme at 50 years of age
MODERATE RISK	Appointment at the Joint Family History Clinic arranged, consultation with both geneticist and surgeon: geneticist explained risks and the surgeon performed breast examination and ordered mammography (wherever appropriate) Follow up at the Family History Clinic arranged as per protocol (usually annual) if all was well.
HIGH RISK	Appointment at the Joint Family History Clinic arranged, consultation with both geneticist and surgeon: geneticist explained risks and offered counselling regarding genetic testing and possible referral for ovarian cancer screening; the surgeon performed breast examination and ordered breast imaging, (with further investigations if necessary). Options discussed included genetic testing, and prophylactic surgery (salpingo-oophorectomy, with input from gynaecologist). Prophylactic mastectomy (with input from plastic surgeon) was discussed with patient after a positive genetic test or sometimes if no mutation result was forthcoming. If a woman declined surgery she would continue with regular surveillance both from the breast and ovarian point of view.

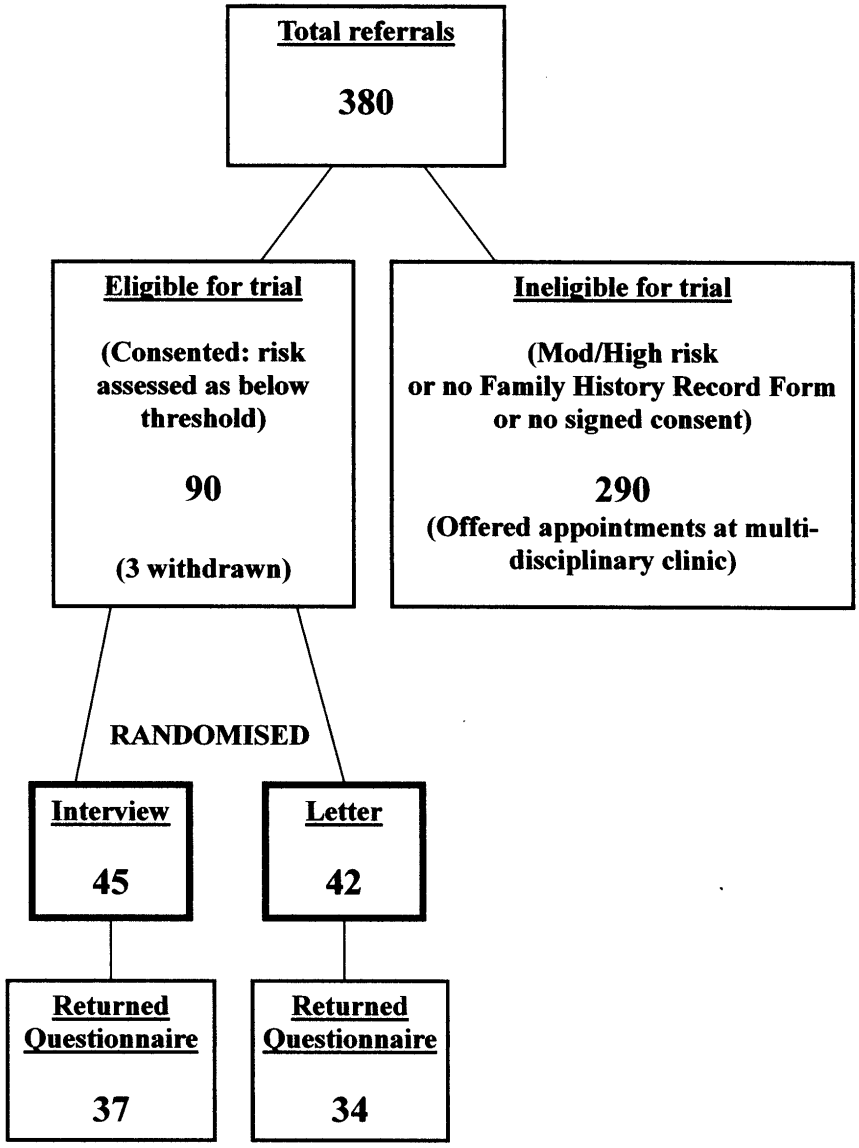

Figure 3.1: Summarised distribution of the referrals and eligibility for the "triage" study period here.

3.3 Detection and recording of cancers in the "family history" clinic

A major purpose of the clinic was to detect breast cancer in women at increased genetic risk at the earliest possible stage, in the expectation that this would minimise the costs and morbidity associated with treatment, while improving prospects of cure. Data from Tayside were collated and checked by myself before being contributed to the EC Demonstration Programme for analysis, thus generating sufficient numbers to evaluate the effectiveness of our own and similar surveillance programmes.

For each cancer diagnosed among patients referred to the breast cancer genetics service, (whether or not screen-detected) information on the method of detection and its management was collected as shown in Table 3.2.

Table 3.2: Data recorded on breast cancers diagnosed among patients attending the breast cancer genetics clinic

- Patient information
  - Means of detection (screen or "interval", mammography/MRI, palpable?)
  - Histological diagnosis and grade
  - Oestrogen and Progesterone receptors
  - Nodal status
  - Patient age at diagnosis
  - Assessed risk status
  - Number of previous screening rounds
  - BRCA1/2 mutation test result
- Management and outcome
  - Surgical procedure as per protocol (lumpectomy, mastectomy, bilateral mastectomy)
  - Radiotherapy
  - Chemotherapy
  - Hormone therapy
  - Annual follow-up data
  - Complications of therapy
  - Local or distant recurrence
  - New primary cancer
  - Death from cancer or other cause

Cancers cases diagnosed through the "old" breast family history clinic (before

1994) were also collected, though it should be noted that the criteria used for enrolment in regular surveillance had been less systematic at that time. Details of all these findings are presented and discussed in Chapter 5.

A related local pilot study, assessing the clinical and economic implications of early detection and treatment of breast cancer in young women, was carried out under my direction. The aim of this small study was to compare the stage, outcome and management costs of breast cancer diagnosed before age 50 years in women who had or had not been enrolled in a regular surveillance programme.

It was hoped that this would provide a base for comparison of the potential reduction in direct healthcare costs if surveillance of those at high risk is effective in achieving diagnosis of breast cancer at an earlier stage of the disease.

3.4 Psychological issues

Within the Triage study, we wished to measure acceptability of managing "low genetic risk" women without offering them appointments at the multi-disciplinary clinic. Women who were eligible and consented to enter the trial were randomised to receive a letter or personal interview for discussion of their risk. They were also asked to complete and return a "satisfaction questionnaire" three months after receiving their risk assessment.

The satisfaction questionnaires were based on the instrument used in the TRACE study in Wales[183] and included standardised and validated measures of psychological health and also specific reactions to the service that they had received (see appendix).

Analysis of the questionnaires was performed using the global experience and satisfaction scores. Statistical analysis of these scores were performed using the SPSS (statistical package for social sciences) programme.

A satisfaction questionnaire was also sent to the referring GPs eighteen months after the end of the study, asking them to complete and return it to Genetics Department. This simply asked for an evaluation of the service provided and specifically whether they had been contacted at any time by women discharged from the clinic, after being told of their "low risk" assessment, with any further

concerns about their risk assessment or any matter related to continuing cancer worry.

Focus groups for Tayside GPs and practice nurses have been planned to obtain their views on the new model for cancer genetic services in Tayside and how the triage model has affected their practice, particularly regarding the management of women at "low" familial risk who may express high levels of cancer-related anxiety. These are taking place at the time of writing.

My own contribution to this element of the study was limited to participation in planning discussions and clinical evaluation of those patients who mentioned breast symptoms during interview with a genetics associate or genetics nurse specialist. Nevertheless, as patient evaluation of the service provided is an important element in judging its cost effectiveness, I felt it right to include a brief account of it in this thesis (see Chapter 4).

3.5 Accuracy of "low risk" as defined by guidelines

In order to obtain information about the true breast cancer incidence among women judged to be at "low" genetic risk (below guidelines threshold for inclusion in a special surveillance programme), records of all such women (who had been referred but discharged) were scrutinised to confirm that the risk assessment had been correct.

Then steps were taken to identify any breast cancers that had subsequently been diagnosed. Initially, this was undertaken in Tayside as a pilot exercise, instigated by myself, using local breast unit records to track subsequent cancers with special attention given for the ones who developed breast and/ or ovarian cancers.

Later, the study was extended to all four Scottish cancer genetics services (based in Aberdeen, Glasgow and Edinburgh, as well as Dundee) and cases of breast or ovarian cancer were traced through the Scottish cancer registry.

The number of women-years of observation within each five-year age group from the age of 30 years was calculated and the expected incidence of breast cancer cases for unselected women in Scotland, within the same age groups,

was derived from National cancer statistics. The findings are presented and discussed in Chapter 6.

3.6 Health economic and management data (sources)

NHS costs for each element of breast cancer management process were extracted, by myself with permission from Dr. John Dewar's study on economic evaluation of the total costs of care of women with breast cancer. Further information was obtained by me from the NHS "Blue Book" for costing (Scottish Health Services Costs Book) and by personal application to Administration Personnel in the Finance Department at Ninewells Hospital (as some of the information required was not listed in the NHS health services costs book).

Existing (limited) publications on the costs and outcomes of various management strategies for familial breast cancer have been consulted. Many refer to healthcare systems that differ fundamentally from the UK National Health Service but they nevertheless illuminate the universal nature of the difficulties faced by those who have to set priorities and to justify expenditure.

The data I have been able to collect both from personal experience and through participation in Scotland-wide, UK-wide and Europe-wide collaborations have generated real evidence that supports some of the recommendations made in the published literature but, more frequently, exposes the frailty of the untested assumptions that underlie many aspects of current practice.

Details of analytical methods and statistical techniques applied are included in the following chapters.

A decision analytical model (decision tree) with current pathways of a patient since referral to the Tayside breast cancer family history clinic was constructed using the DATA 4 (Treeage) analysis programme software[184] with a view to analyse the implications and costs for each pathway of the patient's journey which included decision about genetic testing, prophylactic surgery and breast cancer treatment of patients under regular surveillance through the clinic.

Indirect costs (or impact on productive life of an individual) were not considered for this analysis in view of the difficulties in collecting the data. In fact, indirect costs are considered of debatable relevance in economic evaluations.[93]

The decision analytical model should give evidence on both clinical and economic outcomes of this new clinic model for the Tayside cancer genetics services helping to define best clinical practice and give better resource allocation, identifying parameters that could affect the outcomes.

It became clear after the decision tree had been constructed in quite an extended form, with all options of intervention, that real numbers could not be allocated to every branch of the tree as some of the branches were not discrete options but strategies. Strategies are not allocated numbers from which the "payoffs" can be calculated for analysis of costs and cost-effectiveness.

After revision of the decision tree model, I concluded that patient numbers were too small for complete population of the proposed tree and this approach was set aside for possible future application.

However, costs for each element of the clinical practice (risk assessment, counselling, surveillance, management of cancers and prophylactic procedures) have all been calculated as have the benefits of the cancer family service in terms of earlier diagnosis and prevention of breast/ovarian cancer.

3.7 Personal contribution to related studies in this thesis

1. Since 1991, I have been responsible for the recording of clinical data of the family history patients. Since 1994, I have been the sole breast surgeon in continuous charge of the management of family history patients attending the clinic in Tayside area.

2. I was involved in the planning of all the research elements in the collective studies with colleagues involved in the same field of work.

3. The background reading and writing of introduction, literature review, materials and methods are entirely by myself.

4. In the triage study (Chapter 4), I was one of the grant holders for it and was involved in detailed design of all components of the study. I had sole responsibility for collating and analysing data on clinical investigations (mammograms, additional views, ultrasound, fine needle aspiration, core biopsy) and measuring costs of these procedures. I was co-author on two related publications and first author in the third publication.

5. I extracted, analysed and forwarded to Professor Møller (Norway) all Tayside data on cancers arising among patients enrolled in the breast cancer family surveillance programme. This was a major contribution to the European Collaborative Programme on surveillance for the early diagnosis and treatment of breast cancer in women at significant risk for the disease. I was co-author on three papers published to date arising from this collaboration (Chapter 5).

6. Chapter 5 also deals with the management of women at very high risk (ie. carriers of mutation in the BRCA 1 and 2 genes) and represents my own views drawn from my personal experience of the Tayside clinic and with reference to the European Collaborative study (see above).

7. The studies on the incidence of breast cancer among women judged to be "below the threshold" level of familial risk reported in Chapter 6 were instigated by me as result of my personal observations from the Tayside clinic.

8. I instigated and produced most data for a pilot study which appeared to confirm my suspicion that the actual incidence of breast cancer was higher than predicted by the current guidelines in determining individual's risk for the disease. I played a major role in the subsequent Scotland-wide survey, collecting and verifying all the data from Tayside. I am co-author of one of the resulting publications[185] and a second one recently submitted for publication (authors listed alphabetically by agreement).

9. On cost and effectiveness issues, I undertook all relevant background reading, identified and interviewed individuals with particular expertise to compile and update estimates of all costs incurred in breast cancer screening and disease management. I applied outcome data from the Tayside clinic and from the European Collaborative Programme and then with the

advice of Dr Manouche Tavakoli, my other supervisor, I undertook sensitivity analyses by modifying the most critical parameters in order to reach my own conclusions which I believe represent a uniquely comprehensive measure of the cost-effectiveness of clinical practice in the field of familial breats cancer management. I am first author on a manuscript reporting this work, which is about to be submitted for publication.

10. The overall conclusions from this thesis rest, to a substantial degree, on the original work which I have undertaken personally, as detailed above. That has been supplemented by sharing "the experience of colleagues" for example, the latter part of Chapter 4 and from my reading particularly in the area of quality of life and other psychological aspects of familial breast cancer.

Each of the following chapters relates to one or more of the “Key questions” listed at the end of Chapter 2 and to one or more of the linked studies in which I have participated. Detailed methods are described further in the appropriate chapters.

Chapter 4

Verification of family history

The following key questions have been addressed in this section:

Do GP referrals to the genetics clinics match the established guidelines criteria?

How does accuracy of risk assessment change under different protocols?

What are the costs of enrolling a woman in a surveillance programme? What savings are achieved by more accurate risk assessment? How does this compare with the costs of undertaking that more accurate assessment? What other impact does more accurate risk assessment have on delivery of a breast cancer family service?

These questions translate into the following issues that can be addressed by specifically designed research studies.

The UK-wide survey of breast cancer family history clinics undertaken in 1998, published by Wonderling and colleagues in 2001,[45] indicated that some 26% of referrals did not meet guideline criteria for women at "moderate" (or higher) risk. For the four Scottish clinics, including Tayside, this figure was 33%. That might be taken to imply that general practitioners (particularly those in Scotland) were failing in their "gatekeeper" role.

However, experience in the clinic had convinced me that adequate assessment of familial risk takes a considerable amount of time and, in many cases, requires access to hospital and National records.

GPs themselves have repeatedly pointed out[40–47] that they are ill-equipped to fulfil the role allocated to them in the 1996 Working Group Report and in sub-

sequent guidelines.[38,39] Furthermore as we have recorded in published work, the estimates of accuracy of cases of breast cancer reported by relatives seriously underestimate the potential error rate when compiling an extended family tree.[186] Women are likely to benefit from appropriate genetic counselling that improves their understanding of the concept of risk, helping them in decision making. Genetic counselling requires risk assessment to be as accurate as possible, particularly if it entails recommendations for molecular genetic testing. Assessment of genetic risk status for the disease, should be delivered by a trained healthcare professional with specialised knowledge of the subject area.[179]

Through discussions with Tayside and North Fife GPs at study days and seminars, it became clear that they rarely, if ever, took responsibility themselves for deciding whether or not a woman concerned about possible familial risk of breast/ovarian cancer should be referred to the cancer genetics service. In practice, they referred them all.

I therefore decided, in consultation with my genetics colleagues, that we should carry out a formal assessment of the risk status of all women referred to the Tayside clinic and that the study should record the amount of effort required to reach a confident risk assessment, the costs of that exercise and the implications for cost-effective organisation of the service.

4.1 Evaluation of risk

The Tayside multidisciplinary breast cancer genetics clinic serves a population of around 500,000 and operates within a network of Scottish regional cancer family history clinics.

From 1994, patients who had been kept on regular follow up at a surgical clinic because they reported a family history of breast cancer in their relatives, were given an appointment to the new local joint breast cancer family history clinic (women were seen by both a geneticist and a surgeon at the same session) for formal evaluation of their risks for the disease.

New referrals to the clinic would follow the same process of risk assessment, even if the given information about their family history appeared to place them

in the "low risk" category.

Some of these women had been attending the surgical clinic for follow up for as long as 17 years. Therefore, for the surgeons, those women were not regarded as new referrals. Conversely, all women seen at this new clinic were regarded as "new referrals" by the geneticists as they were seeing them, for the first time, for formal assessment of their risk.

The number of referrals to the joint breast cancer family history clinic increased and the clinic soon became overloaded, with the waiting time for patients soaring far beyond the recommended time to be seen under the government guidance (within 26 weeks from referral; this is due to fall to 18 weeks from December 2006).

The backlog of existing patients to have their outstanding risks assessed was in excess of 400 and there were around 100 new referrals to the clinic per year, requiring allocation of an appointment for formal assessment of their breast cancer risks.

It is important to highlight that in 1994 the distribution of the risk categories into low / moderate / high was somewhat haphazard before formal risk assessment criteria were applied and that probably only 50% of the referrals to the clinic came directly from GPs, the remainder coming via the symptomatic breast service (though the symptoms originally justifying referral were no longer relevant–they had resolved with exclusion of malignancy and, in some cases had been, by admission, spurious, designed to obtain access to mammography).

When a "low risk" assessment was confirmed, further follow up for those women was not required but, in all cases breast examination and sometimes mammography were performed during their consultation at the multidisciplinary breast cancer family history clinic.

With the numbers of new referrals increasing and the existing backlog of patients of previous years to be assessed, the structure of the Tayside clinic needed to be rearranged to ensure that women could be seen within the time recommended by the Government.

We also hoped to address the concerns raised about the potential scale of demand for the service and the apparent social class bias (over-representation of women from social class 1 and a deficit of those from social class 5).[63,187–189]

There is no reason to believe that women at increased familial risk for breast cancer should be found disproportionately in any one social class.

The "Triage" study described in this chapter is of importance as it is designed to assess the efficacy of a Tayside breast cancer family service that imposed limits on the number of women for whom it would be available.

With approval from the Tayside Medical Research Ethics Committee and funding from the Scottish Executive Health Department (Chief Scientist Office) as described in Chapter 1, women referred to the Tayside breast cancer family service were invited to participate in a study of "postal" risk evaluation and, if assessment placed them below the "threshold" level of risk for inclusion in a special surveillance programme, notification of that outcome either by letter or by face-to-face interview.

During the period of thirty months between August 2000 and January 2003, 379 new referrals to the Tayside breast cancer genetic clinic were recorded (303 referrals per year per million population).

Of these referrals, over 75% of the patients came directly from primary care compared with an average of only 49% in the UK survey reported by Wonderling in 2001. We also recorded an increase in referral rate of around 25% since the Wonderling survey data were collected for our region.

Family history questionnaires were returned by 74% of the women referred. The remaining 26% (97) of the women did not return their questionnaires, even after a reminder letter (though many subsequently brought their completed questionnaire to the clinic appointment).

Sixty-five women (23%) who did complete the form did not give informed consent to participate in the trial. In fact, only 18 of the 65 women actively declined participation in the study; the remaining women simply did not return the consent to the study or returned it unsigned.

A clinic appointment was offered to all women who either did not complete the form or declined participation in the study. Breast examination was performed on those women by an experienced breast surgeon (myself) and many of them also had a mammogram prior to discharge to ensure that no breast abnormal pathology was present. Some women brought the signed consent form to enter

the study with them for their clinic appointment but this was too late for randomisation.

In total, two hundred and ninety-one patients were offered an appointment at the multidisciplinary clinic (this included the women who did not return their questionnaires, moderate/high risk patients and women who did not consent to enter the study).

Of the 291 appointments offered, twenty-eight (9.6%) patients either did not attend their clinic appointment on at least two consecutive occasions, despite reminder letters that were sent to them, or cancelled their appointment. Six patients moved away from the Tayside area before their appointment date. Thus, two hundred and fifty seven women were in fact seen at the clinic.

Thirty-seven per cent of women seen at the multidisciplinary clinic (n=94) required no further follow-up either because of their age (having become eligible for the National Breast Screening Programme) (26) or because they were assessed as "below threshold" risk (68).

In total, of the original 379 referrals to the clinic, 155 (41%) women were classified as "low risk" for breast cancer and should, in fact, have been "screened out" by colleagues in the Primary Care setting as described in the current guidelines. Among these, 68 (26.5%) of 257 women seen at the multidisciplinary clinic were at "below threshold" risk for breast cancer.

For the women referred, information was recorded on the source and route of referral as well as on employment status which, together with the women's residential postcode (correlating with deprivation category) enabled us to make a socio-economic profile of the women.[190]

During the period of the study, we found that the social class distribution of women referred to the Tayside breast cancer family service matched that of newly diagnosed cases of breast cancer in the same catchment area.[189]

This contrasted with a comparable audit in 1996/1997, when there was a marked bias towards higher social class, with an excess of women with medical/nursing backgrounds, as also found elsewhere.[187–189]

Of the 217 patients (77%) who consented to enter the trial, a full risk assessment was performed prior to any clinic appointment and of these, 127 patients were

categorised in the "moderate" or "high" risk categories. They were not randomised in the study; an appointment was made for them at the multi-disciplinary clinic.

After full assessment of the women's risks for the disease, 90 (41.5%) were randomised into the study: 42 patients received an explanatory letter about their low risk category and 47 patients were interviewed. (One woman, provisionally assigned to the "letter" group was withdrawn, as explained later).

The term "low risk" was studiously avoided in communication with patients and it was emphasised that all women, regardless of family history, are at measurable risk of breast cancer, hence the need to remain "breast aware".

Of the women interviewed, 45 were discharged from the clinic and 2, initially thought to be at low risk, on interview with the genetics associate had their risk status altered from an initial assessment of "low" to "moderate"; (i.e. some relevant information had not been provided in the returned questionnaire prior to the consultation). These were enrolled in the multi-disciplinary clinic for regular follow up.

All letters sent to the women were copied to their GPs and the GPs were also given a detailed letter explaining the women's risk assessment. It was made clear to the women that any new information about their relatives' cancer history should be notified to the cancer genetic service in order to allow further risk assessment of the individual seeking advice.

Information was also given to them about lifestyle and the need to be "breast aware", and they were encouraged to participate in the National Breast Screening Programme from the age of 50 years. If any breast symptom should develop, they should seek advice from their GP at first instance.

Three women at their interview with the genetic associate mentioned that they had breast symptoms and they were promptly referred to myself, leading to appropriate investigations of the symptoms. As no significant breast pathology was found, all of them remained in the "low risk" category.

One "low risk" woman assigned to receive a explanatory letter was withdrawn from the group as she was found to be affected with breast cancer on examination at the symptomatic breast clinic and, after treatment, was kept on surgical follow up (she had, in fact, reported breast symptoms as well as a positive fam-

ily history, so her planned route was first via the regular breast service and then the cancer genetics clinic).

Thus, eighty-seven of the 379 women referred to the Tayside breast cancer genetics clinic (23%) were discharged from the clinic without clinical or mammographic examinations.

One hundred and ten women were placed on regular annual follow up from their first appointment at the Tayside clinic and 36 patients were temporarily discharged from the clinic as being too young for regular screening. We recommended that they should be re-referred when older, according to our protocol (age 35 years or 5 years younger than the earliest onset in their family).

One patient in the category above was found to have a breast cancer during pregnancy (she was to be re-referred to the clinic for regular surveillance to be initiated when she reached age 34 years, but she was diagnosed at the age of 32 years) and is currently undergoing treatment. Her close relatives' risk will be reassessed in the light of this event.

In view of geographical distance, follow up at Perth Royal Infirmary Hospital (part of the Tayside Teaching Hospitals Trust) was offered to 7 women.

Some of the women were placed on an 18-monthly follow up schedule, alternating with the National Breast Screening Programme because they were still at significant risk for the disease beyond the recommended age (50 years) for discharge to the National Breast Screening programme. (See Figure 4.1)

The questionnaire on family history (see appendix) is designed to be clear and simple. However, it usually requires cooperation between several members of the family and, as a result, discussion about the implications of familial cancer is inevitable. Raising the issue at an early stage of the process rather than later has definite advantages because of the wider circle of relatives that are likely to become involved in due course.

Holloway and colleagues[76] in Lothian demonstrated in a study that the collection of the family history information in advance shortens consultation at the cancer genetics clinic by up to 30 minutes.

With the questionnaires in hand, risk assessment begins with the drawing of the family tree by the genetics colleagues. Once the drawing is completed, the

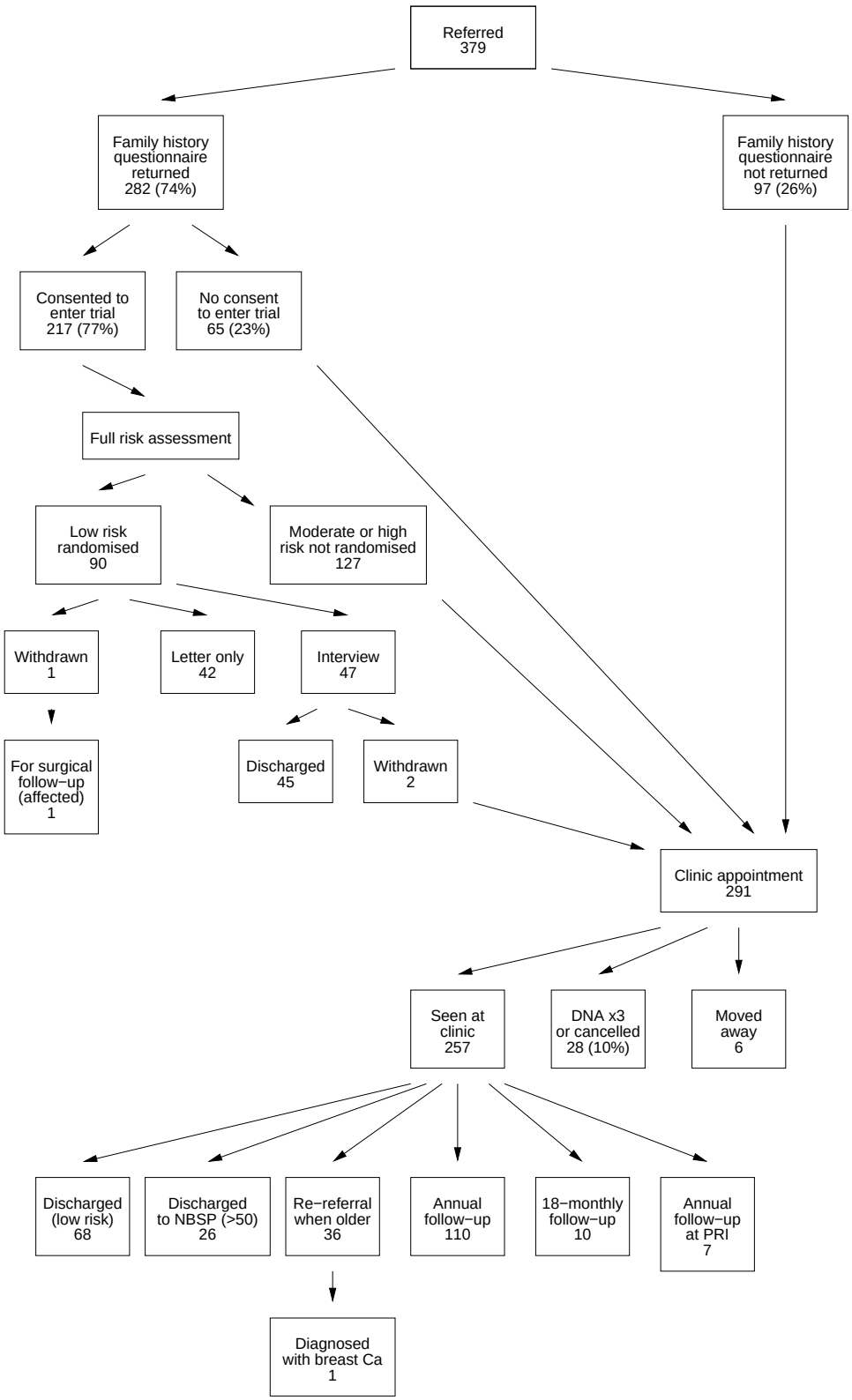

Figure 4.1: Trial Project Summary. This shows the patient's clinic detailed pathway under the new model for the Tayside genetics breast cancer clinic.

genetics colleagues expand the tree (if required) by collaboration with a cancer registry-based genealogist.

Further checks of the information provided are then made by interrogating the Scottish Cancer Registry and/or the records of the Registrar General for Scotland (births, marriages and deaths). The genetics associate can also request permission from affected relatives for access to their hospital notes to obtain pathological details, confirmation of dates of diagnosis etc.

In the Triage study, the extent of this checking varied in relation to the complexity of the given family history. Some of the families' information did not require full check but hospital or official records were consulted for over 50% of the referrals. For example, the genetics associate in Tayside used the cancer registry professional genealogist for 35% of the referrals to the clinic. This service is provided by the Information and Statistics Division (ISD) of NHS Scotland.[180]

Thus evaluation of familial cancer risk proceeded in at least three stages, based on

1. referral letter,
2. family history form, and
3. verification and extension from official records.

The aim of this staged process was to give as accurate as possible a breast cancer risk assessment, though errors could not be eliminated completely. An outcome that was not unexpected was an increase in the proportion of referrals to the clinic that were classified as having a "low" genetic risk for the disease.

The analysis of various stages of the risk assessment process in our local clinic is demonstrated in Table 4.1:

Based on data of 345 consecutive referrals (original 379 minus 34 which were in fact, 28 women that failed to attend their clinic appointment and 6 women that moved away from Tayside area by the time of their appointment). Based on the referral letter (from GP or other clinician) only, the figures show that for one third of the women no level of risk could be assigned, hence the need for further information from the patient by filling the family history questionnaire. Those figures show that for most categories of risk, progress through the three stages

Table 4.1: Percentage of referrals placed in different risk categories at each stage of the assessment process. * Hospital case notes, Cancer Registry, Registrar General's records. Numbers in brackets represent the 95% confidence intervals.

Assigned risk	Information base for risk assessment		
	Referral letter (RL) only	RL + Family History (F/H) form	RL + F/H Form + official records*
Low	25% (21–30)	30% (25.5–35)	40% (36–46)
Moderate	35% (30–40)	57% (52–62)	50% (44–54)
High	6.5% (4–9.5)	6.5% (4–9.5)	10% (7–14)
Unknown	33.5% (29–39)	6.5% (4–9.5)	0 (0–1)

of risk evaluation it results in significant changes in the distribution of the study population in relation to risk allocation.

When the questionnaire was completed and returned to the Genetics service by post, or as we saw, returned during the course of the clinic appointment, all but 6.5% could be allocated to one of the three risk categories.

Hospital notes, Scottish Cancer Registry and public records of births, marriages and deaths were checked and thereafter a more accurate risk level could be assigned to the women seeking advice.

Table 4.2: Sensitivity and specificity of risk assignment

	"Low risk" after full evaluation	"High risk" after full evaluation	Total
"Low risk" after letter alone	84	2	86
"Higher" or "unknown" risk after letter alone	54	205	259
Total	138	207	345

Table 4.2 clearly shows that more women have to be evaluated fully to establish the low risk.

$$\text{Sensitivity of letter alone} = \frac{\text{no. of true high-risk patients detected}}{\text{total no. of true high-risk patients}} = \frac{205}{207} = 99\%.$$

$$\text{Specificity of letter alone} = \frac{\text{no. of true low-risk patients detected}}{\text{total no. of true low-risk patients}} = \frac{84}{138} = 61\%.$$

This ilustrates that GPs tend to err on the side of caution i.e. if in doubt they refer their patients. This may reflect the concept that genetic risk assignement should be left for genetics professionals to perform including the backup access

they have to Cancer Registry and Registrars General records. In fact, the Cancer Genetics team does not know the number of potentially high risk women that are incorrectly screened out by their GPs as a few women are still encountered who were wrongly reassured by their GP, for example when they were told that breast cancer risk cannot be transmitted by a male relative.

The extent of these checks was variable, based on clinical judgement. Table 4.1 demonstrates the changes in distribution of risk categories at each stage of the process (either increasing the risk estimates or decreasing) as the checks continued.

In moving from stage 1 to stage 3, the initial "uncertain" risk category was eliminated but the proportion of "low risk" assessments increased as the process was followed through. However, it is important to note that some of the women considered to be at "low risk" on the basis of GP referral were assigned to a higher category after further checks.

Hence the overall increase in proportion of "low risk" referrals from 25% to 40% does not simply mean that an additional 15% of "low risk" cases were added to the initial set. Accepting the referral letter at face value in order to assign risk would have resulted in several women incorrectly being denied access to the surveillance programme.

Resources for this exercise are not available in primary care and hence the expectations that GPs will be in control as "gatekeepers" in this field should be modified. As noted earlier, several published papers have recorded reluctance on their part to provide this service.[40–42, 44, 74, 191]

As previously mentioned, three out of ninety women, initially judged to be at "low risk" based on the family history form check, had to be withdrawn from the randomised trial because one was diagnosed with breast cancer at the clinic and the other two because their risk level was revised and changed to "moderate" when further information on the family history was elicited at the interview with a genetics associate.

It must therefore be admitted that even very careful evaluation of genetic risk will prove incorrect on some occasions. From the scheme presented in Figure 4.1 and the findings detailed later, we estimate that the error rate (failure to identify "moderate" or "high" risk under the conditions we have applied) is around 4%.

4.2 Cost implications of applying resources to checking family history

A detailed survey of the activities in the multi-disciplinary clinic has been carried out over the Triage trial period. It showed that 54% of "low risk" women seen at the clinic actually had a mammogram performed.

It should be emphasised that these women were seen at the clinic because they could not be randomised in the triage study (either because they had not consented or because they had not returned a completed family history form). In all cases, the intention was to discharge these women after a single visit to the multi-disciplinary clinic.

Additional investigations were required in 18% of the women attending the clinic (overall figure). However, 28.6% (22/77) of women judged to be at "low risk" had additional investigations after a mammogram was performed. While the basic Health Service cost for each visit to a multi-disciplinary clinic is estimated at £25, if a mammogram is carried out as part of the investigations, cost will rise to at least £100, while additional investigations carry the costs shown in Table 4.3.

Table 4.3: Details and costs of the additional investigations performed according to the risk category distribution of the women attending the Tayside clinic.

	Extra mammograms (£80)	Ultrasound (£69)	MRI £400)	Fine Needle Aspiration (FNA) (£100)	Core biopsy (£500)
Low risk	6/42	7/77	0/42	6/77	3/77
Moderate risk	12/106	7/157	2/106	2/157	3/157
High risk	2/24	0/35	0/24	0/35	0/35
TOTAL	20/172*	14/269	2/172	8/269	6/269

* Number of each additional investigation per mammogram performed (extra views or MRI) or per clinical examination (ultrasound, FNA or core biopsy). The costs per investigation were derived from Tayside University Hospitals Trust "blue book".

In the table above, the total number of investigations/ examinations exceeded the number of women seen at the clinic because in some cases women were recalled by the surgeon for further check of their breasts to make sure, for example,

that a cyst that had been aspirated had not refilled or to check that symptoms had settled.

The numbers of mammograms and clinical examinations are not identical because several women had had a mammogram within the preceding 12 months, while others were seen at the clinic for counselling before the age at which mammography would be recommended (normally 35 years).

Particular note should be taken of the "low risk" women examined (77) and those who also had further investigations performed (42 mammograms, 6 extra views, 7 breast ultrasound scans, 6 FNAs and /or core biopsy) as this represents a total cost to the NHS of £8,110 (i.e. an average cost of £119 per each one of the "low risk" women seen at the clinic). No breast cancers were diagnosed among these 77 women.

Substantial costs for the NHS will continue to occur with very little return if women thought not to be at increased risk for breast cancer reach a multi disciplinary breast cancer family history clinic. Many of them will have a mammogram and further investigations performed, as demonstrated in this study.

Reasons for the additional investigations may reflect the need for reassurance of the clinician discharging the women from the clinic that no underlying breast abnormality is present. Furthermore, for many women who did not return the family history questionnaire, the risk assignment could not be completed and confirmed until after the woman's consultation at the clinic. Hence they were managed at the initial consultation as potentially at sufficient risk to warrant inclusion in a surveillance programme.

Since surveillance for women at increased genetic risk for breast cancer is recommended from age 35-50 years, the potential NHS cost for each woman so enrolled is at least £1,500 (£100 $\times$ 15). Thus, if the proportion of referred women who do not require surveillance can be raised from 25% to 40%, savings will be substantial.

For the Tayside clinic, with some 150 new referrals per year, imposing the strict risk assessment protocol described can increase the number of women assessed as "low" risk from 37 to 60. By avoiding the inclusion of these additional 23 women each year, savings of at least £2,300 are achieved in one year and, since surveillance is avoided for a period of fifteen years in each case, the total saving achieved is £34,500 (£2,300 $\times$ 15).

Since we find that the necessary checks can be undertaken effectively by genetics associates/genetics nurse specialists and occupy the equivalent of no more than three sessions per week, the practice is clearly cost-effective.

As noted earlier, we do also rely on input from the medical genealogist at the Cancer Intelligence Unit of NHS Scotland Common Services Agency. However, she provides the specialist service for all four Scottish cancer family clinics (covering colorectal and other familial cancers in addition to breast/ovarian). The Tayside breast cancer family clinic accounts for approximately ten percent of referrals across Scotland to these clinics.

From our experience, an error rate of around 4% for risk assignment is expected even when relying on family history information provided by the questionnaire and subsequently subjected to full checking. This is likely to result in a small number of cancers being missed through failure to provide surveillance where it would, in fact, be justified.

On the other hand, as pointed out earlier, the strict assessment protocol we have described does result in several women being reassigned from "low" to "moderate" or even "high" risk categories.

Thus, sequential checking of the family history information provided is expected to achieve, to a degree, the aim of concentrating resources on those families most likely to benefit from the programme.

Only a long term "follow up" check of the women discharged from the clinic ("low" genetic risk) however will reveal the true incidence of breast cancer in this category.

If we extrapolate our findings (noting that the Wonderling 2001 study[45] found great similarity among the 22 clinics surveyed) then, considering that the total UK population is around 55 million, the number of women referred to breast cancer family clinics each year would be 16,500. If the proportion correctly identified as below the "moderate risk" threshold were increased from 25 to 40% (i.e. 6,600 instead of 4,125–a difference of 2,475) the annual saving to the NHS would be £ 3,712,500 (2,475 $\times$ £100 $\times$ 15).

Even if the total number of clinics operating across the UK increases to between 35 and 40, that still permits substantial investment in professional staff without a net rise in operating costs.

In terms of the key questions set out at the start of this chapter, I have shown clearly that Primary Care is not the appropriate level at which to "screen out" or "screen in" women whose family history would justify inclusion in a special breast cancer genetics service.

The three-stage protocol I have evaluated greatly improves the accuracy of risk assignment while still falling short of perfection. A minimum cost of enrolling a woman in a special "family history" breast cancer surveillance programme is £1500, rising as investigations additional to mammography are included. These costs do not appear to be justified for the majority of women whose family history places them at less than the guidelines “threshold” level of risk.

Applying the three-stage risk assessment protocol described leads to an overall increase of around 15% in the proportion of referred women who could be discharged as falling below the "treshold" risk level. The cost of conducting the formal risk assessment is clearly outweighed by the savings achieved and, in addition, some women who could have been excluded (incorrectly) on the basis of incomplete ascertainment of risk, can now be enrolled in the surveillance programme.

4.3 Patient and GP satisfaction

I collaborated in the following component of the Triage study, addressing the question “How acceptable, to patients and GPs is a system whereby familial breast cancer risk is assessed before any clinic appointment is offered and where women at less than “moderate” risk (not eligible for a surveillance programme) may receive that information only by post?”

A recent meta-analysis of studies on genetic counselling demonstrates that counselling of individuals at increased risk for breast and ovarian cancers significantly decreases general anxiety levels. However, it did not show a significant reduction in psychological distress among those individuals, with conflicting evidence whether counselling actually increases or decreases the accuracy of individuals’ risk perception.[192]

Even though, as explained in Chapter 3, I had only limited involvement in the women’s interviews or giving information of their “low risk” status by letter, I

thought it was relevant to give some consideration in this thesis to the subject of the impact that the information (and hence exclusion from special surveillance programmes) can have. The following section summarises the satisfaction outcomes found during the course of the study.

The women who agreed to participate in the study (investigating the ways of communicating the information that their familial breast cancer risk assessment falls below the current guidelines for management in a secondary or tertiary care setting, by either a letter or personal interview) and who were randomised, received a questionnaire 3 months after their interview or receipt of the explanatory letter, to assess how satisfied they were with the experience of delivery of risk assessment and subsequent advice ("satisfaction questionnaire").

The questionnaire itself was based on one designed and applied in the Welsh "TRACE" study.[78] It comprised well-established and validated psychological measures as well as free-text boxes (see Appendix).

The questionnaire distributed to general practitioners was much simpler, and simply sought their opinions on how the process had affected their own patients (Appendix).

Analysis of the "satisfaction" questionnaire was performed by Dr Gozde Ozakinci from the Department of Health Psychology at the Bute Medical School, St Andrews University.

Seventy-one of the 90 women randomised in the study (79%) completed and returned the three-month "satisfaction questionnaire". Those women had been referred by 82 General Practitioners, of whom 64 (78%) responded to our follow up questionnaires (with replies relating to 69 women - 77%).

In summary, the data showed that the two methods of delivering the information to the participants were acceptable to both the referred women and to their GP's although the women expressed a slight preference for interview.

There was some confusion in the understanding of absolute and relative breast cancer risk information given to the women and this demonstrated that provision of numerical information was unsatisfactory.

Comments in the free text boxes revealed that some women remain convinced that their risk was underestimated, while, conversely, a substantial minority appeared to believe that they were not at risk for breast cancer at all.

Expanding a little on the above summary, some extracted items in the questionnaire showed the following outcomes as quantifiable responses and free text answers to open ended questions:

When asked about breast cancer concerns (6 items) the correlation inter-item was good and the items were averaged to generate an index of breast cancer concerns. No difference between "letter" and "interview" groups was seen: independent samples t-test; $t(69) = -0.636, p = 0.527$.

Ten items were included in the question about actions since referral and correlation among items varied but all were significant. Samples t-test did not reveal any difference between "letter" and "interview" groups. All ten items were tested.

"Women's experiences since referral" had 12 items and correlations between them were all significant so the scores were averaged and an independent samples t-test was used. The difference between averaged scores for "letter" and "interview" groups did not reach significance; $t(69) = -1.676, p = 0.098$.

Independent samples t-test used for the question about "personal breast cancer risk estimate" indicated a significant difference between "letter" group (mean score 2.0) and "interview" (mean score 2.38). Those receiving the risk assessment information at interview, perceived that their risk was slightly higher than those informed by letter; $t(69) = -2.246, p = 0.028$.

When we came to the question of "concern about personal breast cancer risk" the independent t-test showed no significant difference between "letter" and "interview" groups; $t(69) = -0.705, p = 0.483$.

In the "Population lifetime risk of breast cancer" question, respondents were invited to estimate the population risk in two formats. In one of those formats, five responses were missing and therefore only 64 responses were analysed, independent t-tests showed no difference between "letter" and "interview" groups; $t(64) = 0.424, p = 0.673$ and $t(69) = 0.194, p = 0.846$.

The following question on "your own lifetime risk of breast cancer" was also posed in two formats. Five responses were also missing from one of these. The differences were not significant for either format between the groups. Independent samples t-tests were as follows: $t(64) = 1.036, p = 0.304$ and $t(69) = -0.249, p = 0.804$.

Both population and personal risk estimates were inaccurate and the correlations between estimates in the different formats by the same respondent were poor.

In five of the twelve items in the question about "satisfaction with the process", the "interview" group expressed significantly higher levels of satisfaction when compared with the "letter" group (p range 0.020 to 0.001). However, the mean scores for the "letter" group were still between the "quite satisfied" and "very satisfied" range.

None of the differences found between "letter" and "interview" groups were significant when scores were analysed in the General Health Questionnaire for each of the four subgroups. Independent samples t-test was also carried out on each one of them.

The majority of the respondents indicated when answering the open questions, that they were contented with the process, although some of them left the text box blank.

Seven women stated that after assessment they now believed that they were at very "low" risk for the disease, perhaps even below the general population risk (four from the "letter" group and three from the " interview" group). Some extracted answers are shown: *"Quite happy that I am at considerably low risk". "I was happy to learn that it doesn't run in families and I am more relaxed about everything". "Happy to know my risks are not increased by my mother having developed breast cancer".*

A further seven women stated the opposite - that they had not accepted the assessment that they were not at increased genetic risk (four from the "letter" and three from the "interview" group). The extracted answers reflect this: *"I don't know if I believe what you told me; you are giving me a result from statistics which can prove whatever you want to prove. You are not giving me medical facts". "I cannot feel reassured by the response I received".*

No women have complained to their GPs about the way their risk status was assessed or communicated. Only four of the women have returned to their family practitioner with further concerns about breast cancer in the 18-48 months since receiving their clinic report.

Two of them simply wished to have further discussion about the information that they had received from the genetics clinic. The other two women had new breast symptoms (breast discomfort) and these were investigated at the regional breast service. So far no breast cancers were recorded by the women's GPs.

The GPs replies to their "satisfaction" questionnaire revealed that nearly all were completely satisfied with the women's management at the clinic model (62/64).

Two GPs expressed some dissatisfaction with the new clinic model. One of them had reservations in view of the time elapsed between his referral and the communication of the woman's "low" risk assessment (several months). The second GP was dissatisfied because he did not have any record of the outcome of his referral although a copy letter of the outcome was sent to him at the time of the woman's consultation.

Forty-six GPs (72%) had no reservations about the policy of risk evaluation before any clinic appointment was offered to the women referred. Similarly, they accepted that appointments would not be offered to women judged not to be at increased genetic risk for breast cancer (after full assessment) with an explanatory letter being a satisfactory substitute (46/64).

However, 17 GPs had some reservations (one with "serious" reservations) in relation to the difficulty for some women in completing the standard Family History background questionnaire sent to them prior to any appointment at the clinic. Those issues will be discussed further in the final chapter covering recommendations for the future of the service.

Our analysis demonstrates that "postal" assessment and communication of risk status is a feasible and acceptable element of a comprehensive clinical service for familial breast cancer. However, there is a need to improve the explanation of actual risk levels.

This latter finding is consistent with previously published conclusions from several other groups.[193–196] Communication of risk in a clear and rational way is evidently very difficult to achieve.

Further consideration should also be given to the development of healthcare systems that address the needs of women worried about their risk for breast cancer who believe they should be offered more (e.g. formal counselling and

breast screening) from the breast cancer family history service, even though very few are likely to benefit in terms of earlier diagnosis.[197]

4.4 Conclusions

The Triage study has provided some answers to the key questions set out at the opening of this chapter.

Do GP referrals to the clinics match the established guidelines criteria?

Our evidence shows clearly that GPs are right to have concerns about their ability to make accurate assessment of their patients' genetic risk for breast cancer. The figures (Table 4.1) suggest that they tend to err on the side of caution, that is they refer to the Genetics clinics many more patients than the guidelines would justify. This is consistent not only with published reports cited in the thesis but also with informal reports from GPs study days at which they have discussed their practice in this regard.

How does accuracy of risk assessment change under different protocols?

The data summarised in Table 4.1 showed that successive stages of intensification of family history extension and verification lead to increasing accuracy and precision of risk assessment. The Scottish clinics are in particularly fortunate situation in being able to call on the expertise of a medical genealogy service attached both to the Scottish Cancer Registry and the Registrar General for Scotland's records of births, marriages and deaths.

Nevertheless, since this work was completed, there has been a study undertaked in Teeside which showed that deployment of genetic risk assessment professionals ("GRAPS") resulted in an outcome which is almost identical to that recorded in Table 4.1.[198]

What are the costs of enrolling a woman in a surveillance programme? What savings are achieved by more accurate risk assessment? How does this compare with the costs of undertaking the more accurate assessment?

On Tayside, we were able to undertake the complete (3 stages) protocol of risk verification (assessment) for all referrals by using less than 50% of the time of a genetics nurse specialist or genetics associate. The savings amount to approximately £34,500 each year which is considerably more than the salary cost. This

calculation is of course, simplistic, being based simply on the increase from 25 to 40% in the proportion of referrals jugded to fall below the guidelines risk threshold for surveillance.

In fact, the change is more complex because for some patients, the risk assessment was actually increased so that targeting of the screening programme became more effective. At present, it is not possible to attach a monetary value to this aspect of the change.

What other impact does more accurate risk assessment have on delivery of a breast cancer family service?

GPs are very content with the model but the impact on those patients who no longer receive appointment to the multidisciplinary clinic is evidently more mixed. It is clear that a number of them resent exclusion from regular mammography while others misinterpret the reassurance about their level of risk, apparently believing that they are at lower risk than the normal population.

Future work

Our study has not examined an important issue of the practical benefit (or lack of it) to a woman who is enrolled in a special surveillance programme. That issue needs to be addressed and indeed later on, this thesis sets out to do so (Chapter 5).

It is possible that in the future more objective (molecular genetics) methods of assessing inherited breast cancer risk will become the "gold standard" and it will be of interest to compare current indirect methods with these. The concerns of women judged to be at less than threshold risk also need to be addressed to see whether more appropriate provision can be made for them.

Appropriate studies are currently being planned but are beyond the scope of this thesis.

Chapter 5

Cancers detected in the surveillance programme

In this section the questions are as follows:

- What is the rate of detection of breast cancers in young women (35–50 years of age) at increased familial risk undergoing annual screening?
- What is the sensitivity of cancer detection (i.e. rate of interval cancers)?
- Is clinical examination a useful adjunct to mammography in these respects?
- Do screen-detected cancers in this setting carry a better prognosis than non-screen detected? – either in terms of pathological stage at diagnosis or in terms of outcome on follow-up?
- Are there differences in effectiveness of surveillance according to category of genetic risk? If so, are these differences sufficient to suggest that different management strategies may be appropriate for different groups?

5.1 Tayside experience

Cancer case distribution shown in Table 5.1 below reflects the evolution in the assessment of patients at risk for the disease, based on my personal experience

in Tayside. All figures quoted include both invasive cancers and carcinomas in situ.

It is evident from Figure 5.1 that among the "formerly symptomatic" women followed up between 1977 and 1994 because of their family history, several were rather quickly found to have a breast cancer (first visit).

It is difficult, in retrospect, to know what part a suspicion of underlying cancer may have played in the decision to organise regular follow-up, particularly during the period before mammographic screening became routine (late 1980's).

The lack of this important screening tool also accounts for the high proportion of cases during that period who were "symptomatic" at presentation (i.e. they had an abnormality detected by themselves or by the examining surgeon).

Despite the lack of "genetic rigour" applied during the years to 1994, the policy of providing regular follow-up for women with a family history of breast cancer was innovative and has resulted in the Tayside breast cancer family history clinic having probably the longest follow up period in the UK.

With the introduction, from 1994, of formal criteria for assessing women with a family history of breast cancer, there has been a shift in the detection of breast cancers from mainly symptomatic towards screen-detected cases.

The intention was to restrict regular screening to women at significantly increased risk for the disease and enrolment in the surveillance programme has been more tightly controlled since 2000 (as explained in Chapter 4).

Thus the three time periods 1977–1994, 1995–1999 and 2000–present reflect progressively more stringent selection of the screened population (see Figure 5.1 and Table 5.1).

Although interval cancers were detected during each period of the Family History Clinic in Tayside region, in no case had the follow-up interval exceeded the scheduled twelve months. Two of the women had their breast cancer diagnosed at 10 and 11 months prior to their next follow-up appointments.

Two women became symptomatic while waiting to be seen at the clinic, one of them was referred to the clinic and before she was sent an appointment she discovered a lump. This was investigated through the symptomatic clinic and a breast cancer was diagnosed. She was 28 years of age.

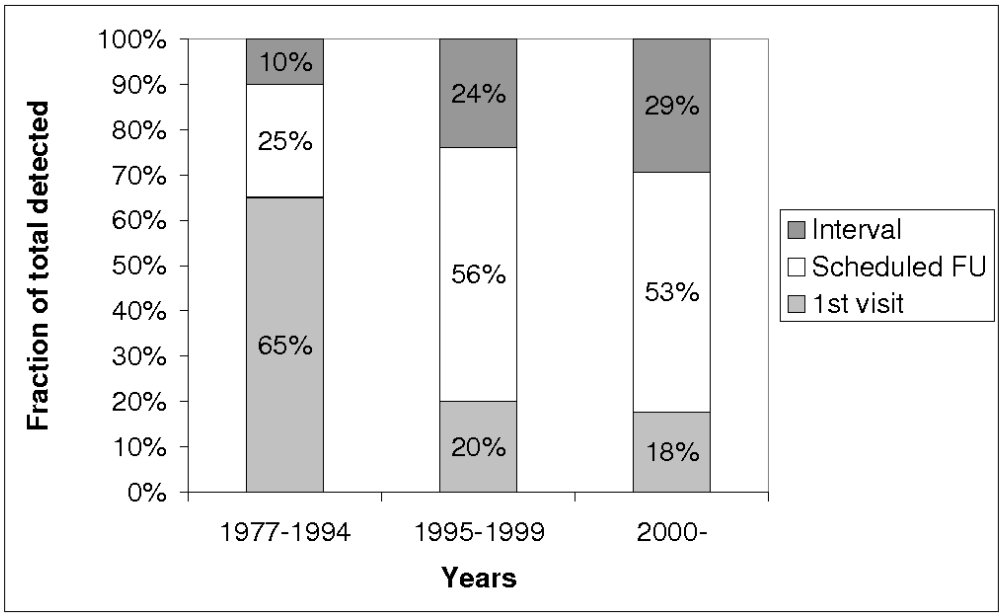

Figure 5.1: Percentage of breast cancers detected as prevalent (first visit) incident (screened) or incidental (interval) tumours according to year of attendance at the Tayside clinic.

The second woman had been seen at the clinic and the recommendation was that she should commence regular screening from age 34 years, she was diagnosed with breast cancer at the age of 32 years.

These two cases of interval cancers diagnosed at such young ages clearly give rise to suspicion of a strong hereditary component.

Table 5.1 summarises the numbers of breast cancers, cancer deaths and mutations detected through the three distinct periods of the Tayside breast cancer family history clinic.

The findings summarised in the above Figure and Table 5.1 are consistent with the view that the application of progressively tighter checks on eligibility for the surveillance programme has meant that fewer "low" risk women have been included.

In the period before 1995, 55% of the breast cancers occurred in this subgroup,

Table 5.1: Breast cancer cases since "family history" clinic started in Tayside.

Period	1977–1994	1995–1999	2000–present
No. cancer cases*	20 patients	25 patients	17 patients
Familial risk levels			
"Low"	11 (55%)	8 (32%)	4 (23.5%)
"Moderate"	2 (10%)	9 (36%)	3 (17.6%)
"High"	7 (35%)	8 (32%)	10 (58.9%)
Age distribution			
Mean	45.7 yrs.	46.8 yrs.	50.4 yrs.
Range	30–72	28–61	32–64
No. (%) <50 yrs old at diagnosis	14 (70%)	15 (60%)	9 (53%)
No. (%) screen detected	8 (40%)	18 (72%)	12 (70%)
No. (%) early stage (T1 or T2, N0)*	13 (65%)	18 (72%)	15 (88%)
No. (%) disease-free at 5 years	19 (95%)	19 (76%)	8 (100%)
BRCA mutations**	1	4**	3
Breast cancer deaths	3	4***	0

*DCIS cases were also included (2/20, 4/25, 2/17). **BRCA1/2 mutations were identified retrospectively until the late 1990s. One patient had mutation on both BRCA1 and 2 genes. ***One BRCA1 mutation carrier. The 5-year disease free survival rate for cancers diagnosed since 2000 can be calculated only for the minority (n=8) who have been followed for five years. Bilateral breast cancer was diagnosed (some were synchronous) as follows: 2 cases in 1977, 1 in 1995 and 3 cases in 2000-present periods. However, for the purpose of this table, calculations are based on the first cancer only.

whereas from 1995–99 and since 2000, the proportion has declined to 36% and then to 23.5%.

This does, however, remain a substantial proportion and begs the question of the real risk of breast cancer in women, with some family history of the disease that are denied access to the surveillance programme. That issue is addressed in Chapter 6.

Whenever patients thought to be at "low" genetic risk were found to have a breast cancer the risk estimate, for them and their close relatives, was changed, as discussed more fully in Chapter 6.

There are no significant differences between the three time periods in mean age at diagnosis of breast cancer, nor in age ranges. For the two later time periods (1995–99 and 2000–present), there are no significant differences in any of the other parameters measured (proportion diagnosed by age 50 years, proportion

screen-detected, proportion "early stage" or proportion disease free at 5 years from diagnosis).

This largely reflects the limited number of cases available for analysis from a single clinic. In order to draw more definite conclusions about the outcome of surveillance for women at increased familial risk, we recognised the need to pool data from several centres operating similar programmes, as described in the latter part of this chapter.

Nevertheless, certain useful conclusions can be drawn from the Tayside data. First, since 1995, 46 breast cancers have been diagnosed in 42 women attending the clinic.

Over that period, we have undertaken almost 8,000 clinical and mammographic screens and, given that the great majority of women attending the clinic are under 50 years old, the expected number of cancers in 8,000 woman years of observation (from the Scottish Cancer Registry data) is about 12.

Thus, women attending our clinic appear to be at least 3.8 times greater risk than the general population. The actual rate of cancer detection (5.8 per 1,000 screens) is perhaps lower than the figure of 8 per 1,000 predicted by Kollias and colleagues[98] but the numbers fluctuate considerably from year to year and are still too small to make a definitive statement on that point.

The proportion of screen-detected cancers correlates well with those diagnosed at an early stage (T1 or T2 and node-negative tumours) and with 5-year disease-free survival.

The findings in these respects are gratifying because in breast cancer, the prognosis is directly related to the stage of the disease at diagnosis as well as the tumour cell biology. Our findings support the earlier report of Kollias and colleagues,[98] who found that surveillance led to diagnosis of breast cancer at an early clinical and pathological stage in young women with a family history of the disease. Prognostic factors are always assessed carefully in any individual who develops cancer.

In breast cancer, axillary node status is perhaps the most important prognostic indicator.[199] Other prognostic factors used are tumour size, histological grading and hormone receptors status.

Prognostic indicators are taken into account in determining the patient's management, for example in the decision whether or not to use chemotherapy, the nature of the drugs employed, as well as the extent of surgery and radiotherapy.

These therapeutic decisions will obviously influence the cost of treatment (as discussed more fully in Chapter 7). More importantly, the prognostic factors relate to the prospect of long-term survival (the term "cure" is perhaps inappropriate in breast cancer which can have an extremely long natural history) and five years disease-free survival is a moderately useful surrogate for that.

Note that, over all three time periods more than half of the breast cancers were diagnosed before age 50 years (compared with approximately 20% of unselected cases).

The prognostic significance of young age at onset is controversial. Several papers have been published on the subject and some have found young age of onset to be an adverse prognostic factor (survival being worse in young, compared with older women with breast cancer). This may well be related to different tumour biology.[99,200,201]

In order to evaluate the results of the "Familial Cancer" surveillance programme, I instituted and supervised a retrospective survey of breast cancers in women under age 50 years who had presented to the Tayside breast cancer service without previously having participated in any regular screening programme.

The study was undertaken by a medical student (Jane Kenyon) as part of her Honours BSc (Med Sci) course and I subsequently extended the analysis, adding material from patients whose notes had been difficult to trace. The study was carried out in 2002 and referred to patients diagnosed before 1997 so that 5-year follow-up data were available.

All details of investigations, surgical and other treatments and associated costs were recorded. These are discussed further in Chapter 7.

Table 5.2 records the major findings in this cohort of 40 unscreened young women with breast cancer, for comparison with the cases identified among women participating in the familial cancer surveillance programme. It is evident that the unscreened group presented with more advanced disease, and suffered correspondingly more recurrent disease within five years.

Table 5.2: Comparison with findings at diagnosis and outcome of young women with breast cancer according to screening history. * Refers only to women with five years follow-up. More years of follow up are required for the surveillance-detected cancers group to allow better evaluation of the Tayside disease-free survival rate.

	Unscreened women <50	Women from familial cancer surveillance programme 1995–present
Number of breast cancers	40	42
No. (%) screen detected	0	30 (71%)
No. (%) early stage (T1–T2 N0)	22 (55%)	33 (78.5%)
No. (%) disease-free at five years	91% for node negative 72% for node positive	*21 (100%) for node negative *6 (100%) for node positive
Breast cancer deaths	3 (node positive)	4 (two cases were node positive, one of the node negative was a BRCA1 mutation carrier)

While these findings may suggest that regular surveillance has been of benefit to the women whose breast cancers were diagnosed within the familial cancer surveillance programme, caution must be exercised because there are some specific indicators that hereditary breast cancer may carry a different prognosis from sporadic cases.

On the one hand, for those with a very strong family history, and hence an increased likelihood of a BRCA1 mutation, breast cancer is liable to develop at a very young age and to be associated with poor prognosis even if detected at an apparently early stage.

It may be that the adverse prognosis for this group is directly attributable to the BRCA1 mutation rather than the early age of onset.[202–205] On the other hand, it has been shown that familial breast cancers **not** attributable to BRCA mutations (i.e. the great majority) tend to have favourable pathological characteristics and hence may carry a better prognosis than sporadic cases.[26,27]

Ideally, therefore, our comparison should be between breast cancers in women

with a family history of the disease who have not taken part in a surveillance programme and those at comparable risk who have done so.

For ethical and practical reasons, however, it is not possible to identify—and follow prospectively—an unscreened cohort of women at increased familial risk.

5.2 European collaborative study data

The Tayside breast cancer family history service formed part of a multicentre European Group (BIOMED 2 Demonstration Programme) from 1996-1999 with the object of assessing clinical services for women with family histories of breast/ovarian cancer.

Since 1999, the group has continued as an informal open collaboration compiling data from patients in whom breast cancer was diagnosed through a surveillance programme. I have been the principal Tayside contact for this aspect of the joint study (see Table 5.3).

Table 5.3: Cumulative data of breast cancers diagnosed under surveillance programme in collaboration with other European Centres. *not reported

	1999	2002	2007
Total cases	161	249	442
No. patients contributed from Tayside	29	40	70
No. patients with BRCA1 mutation	0	36	89
No. patients with BRCA2 mutation	0	8	35
No. patients with no known mutation	0	205	318
% screen detected	75%	nr*	70–80%
% node negative	82%	74%	77%
5 year disease-free survival for CaN0	88%	92%	95%
5 year disease-free survival for CaN+	67%	72%	70%
5 year disease-free survival for BRCA1 mutation	n/a	63%	70%
5 year disease-free survival for no mutation	n/a	91%	92%

The first report[182] included 29 cases from Dundee in a total of 161 (though 32 of these were carcinoma in situ). The mean age at diagnosis was 48.6 years (comparable to our local experience) and 75% were diagnosed in the course of planned investigations as part of their screening programme.

Of these, some 20% of the cancers were identified on clinical breast examination, though they were mammographically occult. That coincides with my own experience in Tayside and with the experience of colleagues in the very large clinic at the Royal Marsden Hospital in London (Dr Ros Eeles, personal communication).

It was noted that the interval cancer rate (i.e. those presenting symptomatically rather than screen-detected) rose if screening interval stretched beyond twelve months. This tended to happen in the early years of service development because facilities became overwhelmed by rapidly rising demand in keeping with the high rate of cancer detection.

Recurrence rates and survival were both related (as expected) to nodal status. Interval cancers were more commonly node-positive (> 40%). The five year disease-free survival was 88% for node-negative cases but only 67% for node-positive tumours.

All these findings tended to confirm the value of regular surveillance for women at increased familial risk of breast cancer, chiefly by demonstrating that the great majority of their cancers could indeed be detected by clinical examination plus mammography and that screen-detected tumours were mainly at an early stage.

However, it was recognised that longer follow-up was required. At that time there were insufficient numbers of known BRCA1 or BRCA2 mutation-carriers identified to draw any conclusions about the efficacy or otherwise of screening for specific risk groups.

By the time of the second report,[48] the number of breast cancers recorded had risen to 249 (including 50 instances of carcinoma in situ), with a mean age at diagnosis of 49 years. Thirty-six patients were known to have had pathogenic BRCA1 mutations but only 8 BRCA2 mutations had been identified.

The BRCA1 mutation-positive cases tended to be of much higher histological grade and were mainly oestrogen receptor (ER) negative, both characteristics implying that they would be more aggressive tumours.

Although a similar proportion of BRCA1 mutation-positive and negative tumours (70%) had no demonstrable nodal involvement at diagnosis, five-year disease-free survival was markedly worse for the former (63% vs 91%). Node-

positive patients, as expected, fared worse, as a group, than node-negative (72% crude survival at 5 years vs 92%).

There were insufficient BRCA2 mutation-positive cases to analyse their outcome separately but the combined findings at this stage showed clearly that BRCA1 mutation-carriers were not adequately managed by annual surveillance since outcome was poor even when tumours were diagnosed at an apparently early stage (small primary lesion without nodal spread).

A striking observation was that patients with BRCA1 mutations who underwent oophorectomy at the time of breast cancer diagnosis (or within 6 months thereafter) had much better survival than those who retained their ovaries. This finding is difficult to explain, given the preponderance of ER negative tumours among BRCA1 mutation carriers.

However, it is in keeping with other reported studies on both preventive effect of oophorectomy in BRCA1 mutation carriers as well as its protective effect against contra-lateral breast cancer.[206]

The third update on this cohort[49] was published after completion of this thesis but, as a major contributor to the study, I was permitted to incorporate the findings into the present work. Essentially, they confirm the 2002 report in relation to BRCA1 mutation carriers and, for the first time, they also showed that BRCA2 mutation-positive breast cancers have a good prognosis when diagnosed within a surveillance programme.

The following information is derived from the analysis of this group:

Møller in collaboration with myself and other Norwegian and UK colleagues[49] collected prospectively data on clinical, pathological and outcomes on all breast and ovarian cancers diagnosed during the course of surveillance programmes from several Family History Clinics until the end of 2005.

The data were analysed in relation to both BRCA1 and BRCA2 mutation status (or none) of affected women, looking into survival outcomes for all the groups.

The conclusion, as previously mentioned, was that potentially good outcomes are reserved for women with BRCA2 mutations when compared with carriers of BRCA1 mutations. The latter unfortunately seem to have worse prognosis even if their tumour is diagnosed at an early stage, but the addition of oophorectomy to standard therapy improves survival.

These series provide for the first time significant evidence for the efficacy of surveillance programmes for breast cancer, based on genetic risk assessment, allowing management of those women to be adjusted accordingly.

Most currently available guidelines for surveillance are based on the, now demonstrably false, assumption that screening has uniform efficacy for all groups of women at increased familial risk. This applies, for example, even to the 2006 report of the American College of Physicians.[1]

The most important new finding[49] is the good outcome of surveillance for women with BRCA2 mutations as well as for mutation-negative patients, and the lack of correlation between stage at diagnosis and outcome (for BRCA1 mutation-carriers only).

Tayside patients have been included in the large multi-centre UK trial of MRI for women at increased risk of breast cancer (MARIBS). Data emerging from this and other trials from around Europe are demonstrating that this method is very efficacious in detecting small carcinomas, particularly for BRCA1 mutation carriers.

The recommendation seems to be that this subgroup should have MRI scanning performed every six months.[50,203,207] However, funding is not yet in place to implement that policy across the UK.

Further information on the regular use of MRI (Magnetic Resonance Imaging) as screening tool for "high risk, BRCA1 mutation carrier" women is awaited as the lack of correlation between tumour stage and outcome means that even earlier detection of cancer may not improve survival. Longer follow up is required of MRI-detected cases to address this issue.

5.3 Surveillance of women at high risk

As demonstrated in Chapter 4, the great majority of women referred to the Tayside Familial Breast Cancer service are at "Moderate" rather than "High" risk. The latter category is defined by having a family history that predicts a likelihood greater than 60% that a predisposing cancer gene mutation of high penetrance is present (in the family). That in turn translates into a history of four or more close relatives (one first degree, or second degree via an intervening male)

with breast cancer or ovarian cancer or one first-degree relative with both breast and ovarian cancer. Evidence has been presented earlier in this chapter that carriers of BRCA1 mutations are not adequately protected by regular annual breast screening, but require alternative management. Furthermore, BRCA1 mutation-carriers are liable to develop breast cancer at a particular early age. Thus, there are sound reasons for investigating "high risk" women as a matter of urgency, with a view to identifying as many BRCA1 mutations as possible.

All women assessed to be at "high"genetic risk for breast/ovarian cancer were offered regular surveillance through the Tayside familial breast cancer clinic and were counselled by the geneticists on the availability of tests for specific gene mutations. The implications of such testing and the limitations of the procedure were explained in detail.

Only recently MRI scanning became available for women at high genetic risk for breast cancer (women carrying a genetic mutation in one of the genes causing breast cancer; eligible women who declined genetic testing; women belonging to families that indicate a probable genetic fault but in which there is no surviving relative to be tested or in which relatives have been tested but no genetic abnormality had been identified).[70,130,207] At the time of our study period, women were not routinely screened by MRI (only if participating in the MARIBS study), in view of the outcomes published recently there is great pressure to get this investigation incorporated into the currently run screening programme for high risk women. This unit (Ninewells) is now in the process of selecting eligible indviduals who will meet the current recommendations. Longer follow-up is required for this group of women undergoing MRI screens, particularly BRCA mutation carriers, as the possible survival benefits are still unclear. MRI scanning could also generate unecessary anxiety as it could lead to unnecessary biopsies.

From 1994 to 1999, mutation testing was essentially funded through research grants and was undertaken independently in molecular genetics laboratories in Aberdeen, Dundee, Edinburgh, Glasgow and St. Andrews, though there was a high degree of cooperation between the centres, leading to the publication of a compilation of over 100 BRCA1 and BRCA2 mutations detected in Scottish and Northern Irish families.[21]

Given the restricted resources for these studies, it is not surprising that discovery

of a given mutation could take several years and great patience was required on the part of both patients and clinic staff. Even in 2006, it remains extremely difficult to find certain mutations –for perhaps 15% of cases in which there is virtual certainty that a BRCA mutation is present, current techniques fail to find them. This applies even to the "state-of-the-art" commercial facility at Myriad Genetics Inc. in Utah. Despite the long waiting time for results in the UK, requests for testing at the Myriad facility (which undertakes to complete the process in a few weeks) have been very rare in Scotland. There have been none from the Tayside clinic.

From 2000 onwards, the laboratory service for detection of "cancer gene" mutations in Scotland has been funded through the Molecular Genetics Consortium (part of the Common Services Agency of the NHS Scotland) and BRCA mutation-detection has been the responsibility of the Aberdeen and Glasgow laboratories, working in partnership.

The first requirement for molecular screening is a living affected relative. Unfortunately some patients do not have any surviving relatives who can be asked if they are willing to give a blood sample for genetic testing for BRCA1 and BRCA2 mutations. It is possible that, as technology advances, DNA extracted from fixed tissue blocks (e.g. lymph nodes) removed at surgery, may be acceptable material for that purpose but at present this is only attempted in a research setting.

Once a result had been obtained, the affected relative was informed of it and information was shared with the family. If she tested negative for the genetic fault, after completion of the full screen of BRCA1 and BRCA2, an undertaking was given that, if this was the family's wish, as new diagnostic techniques became available, the DNA would be tested further in the hope of eventually identifying the precise cause of the "high risk" cancer pattern – either a "difficult to detect" BRCA mutation or an alteration in a currently unknown "cancer gene".

If a pathogenic mutation had been found, the patient who had originally sought advice about her genetic risk was given further counselling about genetic testing and its implications for themselves and other family members, before deciding whether to proceed to formal testing of her own mutation status.

The option was given to discuss prophylactic surgery even before taking the decision whether or not to have the "gene test" but, in my experience such discussions usually follow rather than precede testing.

The technical procedure for molecular testing is relatively simple once the precise mutation in the family is known, since only the affected region of one gene has to be sequenced. Results are provided within six weeks and practice in the Tayside clinic has always been to give the result in the course of a face-to-face interview, where the patient is accompanied by a partner, relative or by a friend.

During the 30 months period of the "Triage" study, 21 women (from a total of 33) considered to be at very high genetic risk for breast cancer were offered genetic testing through our clinic.

One woman declined to be tested and remains on regular follow-up. Another woman tested negative for the genetic fault found in her relative and this puts her in the "population average" risk category. She has since been discharged from follow-up.

Two women who underwent genetic testing were found to carry the same mutation as their affected relative. Unfortunately, no blood sample was available from relatives of 12 women considered at "high risk" for the disease as there was no living affected relative to be tested for BRCA mutations.

Over the same period, sixteen women (5%) considered at increased risk for breast and other cancers in the Tayside genetic clinic were referred to other specialists (referral would also include their relatives).

Thirteen women were referred to the gynaecologists to consider ovarian cancer screening or prophylactic surgery, three to colorectal surgeons for investigation of possible hereditary non-polyposis colorectal cancer syndrome–HNPCC.

5.4 The place of prophylactic surgery

With the increase in knowledge of hereditary breast cancer risk the relative merits (or otherwise) of different options (surveillance or prophylactic intervention) available for women referred to the cancer family clinic ought to become clearer but, in fact, the necessary evidence is proving difficult to compile. The following questions are relevant, though answers are currently far from complete:

1. How do women in Scotland react to discussions of prophylactic oophorectomy and/or prophylactic mastectomy?

2. What is the take-up rate for surgery and at what age?

3. Is uptake of prophylactic surgery related to objective estimate of risk or to family responsibilities (young children, etc) or to other identifiable factors such as social class?

4. On follow up, are women satisfied with the results of the surgery and, (if possible) how content with their decision are women who opt not to proceed to surgery?

Cost/ benefit issues in relation to prophylactic surgery or screening are covered in Chapter 7.

As discussed in Chapter 2, bilateral prophylactic mastectomy has been shown to be highly effective in providing long-term protection against breast cancer for women at very high genetic risk. Before the BRCA genes were discovered, a few women with very striking family histories opted for this procedure, even though their own risk of carrying the (then unknown) causal mutation could not have been greater than 50%.

In such a setting, it could be argued that the surgery was treating anxiety as much as preventing cancer. However, anxiety can be very debilitating and, given the family situation, the decision to proceed with total removal of the breasts is defensible.

In recent years, the technical aspects of total mastectomy and reconstruction have advanced considerably and greater numbers of women at high risk are now in a position to know their own genetic status. Furthermore, the findings of the European Collaborative Group set out earlier in this chapter indicate that, for BRCA1 mutation-carriers, annual surveillance alone provides inadequate protection.

In my experience, patients at high risk are willing to consider prophylactic surgery, yet the uptake is still very low. There is almost certainly a "cultural" component in this decision and therefore clinicians must consider the women's values and cultural background as well as her personal preferences when discussing with them the issues of prophylactic risk reducing interventions.

Issues arise in relation to the long-term impact of breast removal on women's sexuality and psychosocial consequences both of the surgery and of their mutation carrier status.

In the McLeish study (2003),[189] the proportion of women from the Tayside clinic opting for prophylactic surgery was small in comparison to other centres in England and other European countries. There appeared to be unrealistic expectations of mammography and little perception of the relative value of prophylactic surgery among the risk-reducing measures currently available.

McLeish also found that a third of the women in the survey considered prophylactic surgery to be "not really acceptable" or "unacceptable". These findings were similar to those of Meijers-Heijboer et al. (2000)[208] in the Netherlands.

This makes the demand for prophylactic breast surgery considerably weaker than for mammography. McLeish also found that attitudes to prophylactic ovarian risk-reducing surgery were guarded, though more favourable than towards prophylactic mastectomies.

In France, Eisinger et al. (2000)[209] reported that only 4.7% of the women in their study found it acceptable to consider surgical intervention as a cancer risk-reducing measure in young women. When a causal BRCA mutation has been demonstrated, however, attitudes to surgery may change and the Dutch group led by Meijers-Heijboer (2000)[208] found that as many as 51% of such women would opt for prophylactic surgical intervention.

No form of prophylactic surgery should be treated lightly and total mastectomy with reconstruction of the breast is a major procedure. It is therefore important to alert women to the real risks of such interventions before they are asked to take a decision. For example, there can be surgical complications, varying from haematomas or infection to failure of reconstruction, requiring removal of implants or reconstructed breast tissue (in the case of reconstruction failure).

Even in the technically simpler case of oophorectomy, complications can include infection, bleeding, urinary and/or bowel injuries and, of course, premature menopause which may require a period of hormone replacement therapy. All of these possible complications (together with the natural reluctance to go "under the knife") no doubt contribute to the limited uptake of risk-reducing surgery.

To date, I have not detected much shift in attitudes but the disappointing outcome of regular screening for BRCA1 mutation-carriers has not yet been publicised and is only beginning to be disseminated through the clinic, so attitudes towards surgical intervention to reduce cancer risk may change. Furthermore, with the prospect that the NICE guidelines on inherited breast cancer may be adopted widely across the UK (including Scotland), the proportion of "high risk" women eligible for genetic testing will be higher than at present (under SIGN guidelines).

This may contribute to an increase in numbers of known mutation carriers. Overall, therefore, I expect demand for prophylactic surgical interventions to increase substantially in the future (as discussed above).

Since the study commenced, two women found to carry the same (BRCA2) mutation as an affected relative, have discussed prophylactic bilateral mastectomies. Only one has undergone the procedure to date. I ought to highlight that the number of women being considered for bilateral prophylactic mastectomy has increased gradually over the past decade. However, the number of women who decided to go ahead with surgery remains very low.

While the foregoing refers to prophylactic mastectomies in women who are aware of their "high risk" status but are disease-free, there is a second category of women for whom preventive mastectomy is considered, namely "high risk" women who have already been diagnosed with unilateral breast cancer, have had their primary cancer treatment but seek advice on risk-reducing surgery for the contra-lateral (unaffected) breast. This would also include those who, some time after their breast cancer treatment, were found to carry a mutation in one of the BRCA genes.

It is understandable that patients, who have already experienced cancer, may be less reluctant to contemplate the drastic measure of complete breast tissue removal. Most of them are satisfied with their decision to undergo the procedure.

A study by Geiger and colleagues[210] has demonstrated contentment with the decision to have prophylactic contra-lateral surgery in 86.5% of their cohort (n=371) and also reported contentment with subsequent quality of life (comparable to that of breast cancer survivors who had declined risk reducing surgery). However, their study results applied to a wide range of women with breast cancer diagnosis and because the study had little information on patients with fam-

ily histories of breast cancer, the results may not apply specifically to "high risk" breast cancer women.

Since 1994, eleven patients from the Tayside breast cancer family history clinic were treated for breast cancer and subsequently have had prophylactic contra-lateral breast surgery. In two of these, an unsuspected carcinoma was found on pathological examination of the removed tissue. Neither was an invasive malignancy (they were DCIS) and both patients remain on regular follow up. One has a BRCA1 mutation and the other BRCA2. One other patient who had contra-lateral prophylactic surgery has since died from metastatic breast cancer. She was a BRCA1 mutation carrier.

Of those eleven patients with previous breast cancer and who underwent contra-lateral prophylactic mastectomy, four were known to carry a mutation; one of them in fact had mutations in both BRCA1 and 2 genes.

Although data were not formally collected, in informal conversations with those individuals it emerged that the major factors influencing their decision to undergo the procedure were: a) molecular confirmation of their high risk status and b) perceived needs of their family—particularly their commitments to the raising of children.

The mean age for undertaking bilateral prophylactic mastectomy in women who had previous breast cancer diagnosis was 45 years (range: 34–59) and, for those undergoing prophylactic mastectomy only because of their high risk status (no previous breast cancer), it was 44 years (range: 36–56; there was no significant difference between the two groups).

5.5 Bilateral salpingo-oophorectomy

Ovarian cancers are still being detected at advanced stages of the disease as clinical manifestations of ovarian malignancies are only apparent late in the evolution of the disease.[61,159,160] It is clear that the current available methods of surveillance for ovarian cancer are neither sensitive nor specific and perhaps give false reassurance on the basis of negative test results.

Nevertheless, as discussed above, the McLeish study,[189] based on Tayside and Lothian, in keeping with findings from other European centres, recorded general

reluctance to consider prophylactic oophorectomy as an alternative to screening.

Patients at moderate or high risk levels for ovarian cancer were given the opportunity to see a gynaecologist with a special interest in inherited ovarian cancer, for discussion of the options currently available for both surveillance and risk reducing surgery. Unfortunately colleagues in Ninewells Gynaecology Department do not keep a structured database of the patients referred. I am currently addressing this and plan to collect more comprehensive prospective and retrospective information on the patients.

From the Genetics Department in Ninewells, from 2000 to the end of 2003, 112 patients from 76 families, judged to be at significant risk of ovarian cancer, were referred to the Gynaecology Department to discuss the pros and cons of having ovarian cancer screening or risk reducing surgery.

Of these, only 28 patients have undergone bilateral prophylactic salpingo-oophorectomies: twelve were mutation carriers, eight of whom had previous breast cancer treatment. Four of these women did not have previous breast cancer. The remaining cases were at high risk of developing breast and/or ovarian cancer. (Table 5.4)

Table 5.4: Bilateral salpingo-oophorectomies carried out in women attending the Tayside breast cancer family service.

Patients undergoing salpingo-oophorectomy	28
BRCA1 or 2 mutation carriers	Previous breast cancer: 8 No previous breast cancer: 4
Non-mutation carriers (i.e. no mutation yet identified)	Previous breast cancer: 3 No previous breast cancer: 13

Until relatively recently only the ovaries were removed, usually by a laparoscopic approach. With the increased recognition that fallopian cancers are also related to inherited ovarian cancer, it is now common practice to remove the fallopian tubes at the time of oophorectomy, particularly for proven BRCA1 and BRCA2 mutation carriers.

One patient, known to be a BRCA1 mutation carrier, who underwent prophylactic bilateral salpingo-oophorectomy in 2003 and bilateral prophylactic mastectomies in 2004 has since presented with ascites and further investigations reveal

that she has primary peritoneal carcinomatosis. She is the first patient from our series to have developed malignancy after prophylactic oophorectomy, though it is a well recognised danger, as discussed in Chapter 2. It happens that this patient was found to have a borderline ovarian tumour at the time of her prophylactic oophorectomy. Current thinking suggests that borderline ovarian cancers are unrelated to BRCA1 or 2 mutations so the significance of this finding is unclear.[61]

One other patient who had undergone prophylactic bilateral salpingo-oophorectomy recently presented to the breast clinic with a locally advanced breast cancer and is currently undergoing treatment. She carries a mutation in the BRCA1 gene. This highlights the fact that oophorectomy, though it is a useful measure for reducing breast cancer risk in BRCA1 and 2 mutations-carriers[158,159] does not completely abolish it. A residual 30–50% of a pre-existing large risk is still substantial. This particular lady has had several consultations in the past to discuss prophylactic bilateral mastectomies but declined to have it performed as she was reluctant to "lose" the nipple and areolar complex as part of the proposed surgery.

As in prophylactic mastectomy, the uptake of prophylactic salpingo-oophorectomy in this series seemed mostly related to knowledge of molecular identification of a genetic BRCA fault, previous diagnosis of breast cancer and family related reasons.

The knowledge that ovarian screening is not as effective as breast surveillance and that prophylactic oophorectomy does not have a cosmetic impact (in contrast to prophylactic mastectomy) means that oophorectomy is more acceptable for women seeking advice on prophylactic surgical intervention despite potential problems with menopausal symptoms.

The mean age for women undergoing bilateral salpingo-oophorectomy was 47 years (range: 33–62). Unfortunately complete data were not available on 7 cases, so that calculation was performed for only 21 women. Of the patients (28) who underwent prophylactic oophorectomies, 12 were proven mutation carriers, (10 BRCA1 and one BRCA2) plus another who had a mutation in both BRCA1 and BRCA2 genes.

5.6 Conclusion

The questions posed at the beginning of this chapter are listed again and a summary of our studies conclusions were:

What is the rate of detection of breast cancers in young women (35-50 years of age) at increased familial risk undergoing annual screening?

We find that the rate of cancer detection is 5.8 per 1000 screens and we would anticipate that the rate will rise as tighter criteria are applied for inclusion in surveillance programmes and as more BRCA-mutation carrying families are identified. This compares with the target rate for the National Breast Screening Programme (for women over 50 years of age) of six breast cancers per 1000 examinations. Although the NBSP is referring to three-yearly rather than yearly examination. Despite the recognised stress associated with regular screening and the unavoidable instance of further investigations which ultimately prove negative, it is clear that women at increased familial risk of breast cancer value access to a screening programme and many studies have shown that the overall psychological impact is at worst neutral.

The evidence that regular screening leads to diagnosis of breast cancer at an earlier stage must, at present, be interpreted with some caution since the comparison group (women diagnosed before age 50 years without having participated in a regular programme) were not selected on the basis of family history and were presumably mainly sporadic cases. As such, the biological behaviour of their cancers may not have been entirely comparable to those of the "family history" group.[27]

What is the sensitivity of cancer detection (i.e. rate of interval cancers)?

Sensitivity (at 70-80%) of screen detected cancers is marginally lower than the target for older women in the NSBP which probably reflects the greater technical difficulty of detecting small cancers in mammographically dense breasts of young women. It is notable that when screening intervals extends much beyond 12 months, the rate of interval cancers rises substantially. MRI has been shown to improve sensitivity of breast cancer detection particularly for women at high genetic risk for the disease but it is time consuming and expensive (it takes about 1 hour to complete the investigation and further time is given for analysis of the images obtained). Its impact on overall survival has not yet been measured.

Surveys (including one from Tayside and Lothian) have shown, however, that there may be an unjustified belief in the "magical" properties of mammographic screening so that many women will choose regular surveillance over prophylactic surgery. In fact, mammography alone as a tool for screening women at increased risk of developing breast cancer is not advisable as some cancers could be missed if only mammography is used.

Is clinical examination a useful adjunct to mammography in these respects?

Our data strongly support inclusion of clinical examination. About 20% of cancers are detected b clinical examination in addition to mammography. Furthermore, the opportunity to discuss concerns with the breast surgeon or experienced breast care nurse must improve the experience of surveillance. The combination of both breast examination and mammography is the best method of screening women at increased breast cancer risk currently available. The use of MRI is still being analysed as part of a UK-wide trial of screening "high" breast cancer risk women to which I have contributed.

Do screen-detected cancers in this setting carry a better prognosis than non-screen detected? – either in terms of pathological stage at diagnosis or in terms of outcome on follow-up?

On both counts, screen detected cancers do better. Over 40% of interval cancers (i.e. not screen detected) were node positive compared with 25% of all cancers in this cohort.[182] All 3 of the reports of the International Collaborative Group (in which I collaborated) confirm that node positivity equates to worse survival. From the information that emerged via the European collaborative group, it is now clear that, for BRCA1 mutation carriers, conventional mammographic and clinical screening should no longer be considered a "safe" option, in view of the high incidence of cancers and their poor prognosis despite apparently "early" detection. Prophylactic surgery is of proven protective value and would be the best currently available strategy for those patients.[48,49] The studies described in this chapter demonstrate that regular surveillance for women with a family history of breast cancer is associated with detection of the disease at an early stage and (excluding BRCA1 mutation-carriers) with a good outcome well beyond five years.

Are there differences in effectiveness of surveillance according to category of genetic risk? If so are these differences sufficient to suggest that different management strategies may

be appropriate for different groups?

One of the most important outcomes of the work reported in this thesis is the very clear demonstration[49] that despite detection of cancers at an apparently early stage, carriers of BRCA 1 mutations have a significant worse outcome than those with BRCA 2 mutations or no demonstrable mutation. The implication is that unless MRI or other new screening modalities change the outcome for women carrying BRCA 1 mutations, prophylactic surgery is a very realistic option for them. They, however, benefit from oophorectomy at the time of the diagnosis although their tumours are usually ER-negative.

Prophylactic surgical intervention is a serious option for those at very high genetic risk for the disease and at present prophylactic bilateral salpingo-oophorectomy is much more acceptable to Tayside patients than prophylactic total mastectomy. This probably reflects a "cultural norm" for those women. In Tayside, the uptake of prophylactic bilateral mastectomy has been low; probably because the nature and scale of this intervention is seen as very disturbing, specifically with regard to body image and sexuality.

Women at “high” genetic risk, who have been diagnosed with unilateral breast cancer are evidently more prepared to contemplate prophylactic removal of the unaffected breast.

The intervention of bilateral salpingo-oophorectomy appears to be rather more acceptable to the patient, perhaps because it has been suspected for some time – and increasingly evident from experience over the past years - that this procedure is much more effective than screening, not only reducing ovarian cancer risk but also providing measurable protection against breast cancer.[158, 168, 206]

All Tayside patients offered the option of prophylactic surgery (either mastectomy or oophorectomy) were at high genetic risk. However, of those who proceeded to oophorectomy, 12 of 28 were known carriers of BRCA mutations. There is indication that molecular confirmation of “high risk” status increases the likelihood that the patient will proceed to prophylactic surgery.

Similarly, of the patients who have had unilateral prophylactic mastectomy after diagnosis of cancer in the contra-lateral breast, 8 out of 11 were known mutation-carriers. Five women underwent bilateral prophylactic mastectomy; only one of them carried a proven BRCA mutation.

As mentioned before, formal data were not collected regarding the reasons that led to the decision of prophylactic risk reducing intervention. After informal conversation with those individuals some reasons were given - mainly the knowledge of their molecular "high risk" status, family related considerations and previous breast cancer diagnosis.

The mean age for women having prophylactic salpingo-oophorectomy was calculated for 21 patients (data were not available for 7 patients) and not surprisingly was at slightly older age (mean 47 years: range 33–62) than the ones having prophylactic mastectomy (45 years for the affected women having contra-lateral breast cancer and 44 years for the ones having prophylactic mastectomy in view of the risk status).

Knowing what we do know about the inadequacy of current breast screening protocols for BRCA1 mutation- carriers and the poor sensitivity and specificity of annual ovarian screening (specifically for premenopausal women) there is perhaps a need to reconsider the "non-directive" counselling approach process for women at high genetic risk.

Reluctance to contemplate major prophylactic surgery is understandable but there is an onus on the part of those of us who accept responsibility for the management of women at increased genetic risk to ensure that, in presenting options to them, the relative efficacies of these options, their limitations and the possible complications are all clearly understood.

5.7 Future work

Longer-term follow-up is still required to establish the true value of surveillance programmes because breast cancer is a disease that can recur many decades after its treatment and because the numbers, particularly of BRCA 2 mutation-carriers, are still rather low to convince doubters that their outcome in a screening programme is very different from that of BRCA 1 mutation-carrying individuals.

MRI detected cancers must be followed up to determine whether earlier detection leads to significant improvement in outcome, particularly for BRCA 1

mutation-carriers as currently they fare worse even if their disease is detected and treated early.

The development of newer forms of treatment for established breast cancers (for example the use of platinum-based cytotoxic chemotherapy agents) may have a significant impact in outcome of BRCA 1 mutation positive carriers and this must be kept in mind so that future guidelines can be modified accordingly.

We need to look more closely at women's attitudes to prophylactic surgery and devise effective ways of presenting the options clearly but without inducing disabling anxiety. Studies looking at the long-term effects of those interventions are currently being planned but are beyond the scope of this thesis.

Chapter 6

True incidence of breast cancer in "low risk" women up to age 55 years

This section of the thesis deals specifically with the question:

Are current settings for the actionable risk "threshold" valid?

Published guidelines (NICE and SIGN) recommend that women concerned about their risks for breast cancer and/or ovarian cancer should, at first instance, seek advice from their primary care team who should perform initial risk assessment and only those with an assessed risk above the specified threshold should be referred to specialist services for appropriate screening, counselling and possible interventions aiming to reduce their lifetime risk for the disease.

Over the years, data were gathered on any breast cancer that was detected among women who had been referred to the Tayside familial breast cancer service. This included information from the period 1977–1994 when surgeons in Tayside were perhaps pioneering regular surveillance for ladies with a family history of breast cancer in the UK.

As previously mentioned, unlike the practice since 1994, no strict criteria were followed to enrol those women in a regular surveillance. Since 1994, when a more structured clinic for women at increased familial risk for breast cancer was developed in Tayside with input from geneticists, there has been formal risk assessment of the women referred to the clinic.

Through my direct involvement in the Tayside symptomatic breast service, I noted that several patients discharged from the " cancer family" clinic, as being

below the required level of familial risk for enrolment in regular surveillance, were later presenting with breast cancer. Many of these patients had been referred via the symptomatic clinic (pre-1994) but there were some who had attended the family history clinic after 1994, who had never complained of any breast symptoms.

I therefore decided to investigate the true incidence of breast and /or ovarian cancer in women thought not to be at significantly increased familial risk. My suspicions that there could be flaws in the currently used guidelines to identify "low" risk women were supported, but only much later, by the report of Amir and colleagues,[211] to the effect that most commonly applied models to assess and predict breast cancer risk from family history tended to underestimate the true risk. They reached their conclusions from a prospective evaluation of five such protocols. The underestimation was more apparent in women at the "lower" end of the risk spectrum. However, the numbers were rather small to power the conclusions.

An initial pilot study, carried out only among Tayside clinic referrals, did seem to indicate that the actual risk to these women was greater than 1.7 times the (age-matched) general population level quoted in most guidelines as the "threshold" for enrolment in a regular surveillance programme.

However, the numbers were not large (8 cancers expected, 17 observed) and I could not guarantee that all cancers had been recorded since I could only include those presenting to the Tayside breast surgery service. In addition, some of the cancers recorded were in women who had originally presented with symptoms before 1994 (see Chapter 5), which might have influenced the incidence of tumours.

I therefore asked colleagues from the other 3 Scottish centres holding a family history clinic to collaborate with the Tayside group, providing information on the number of breast cancer cases detected in their "low risk" women cohort. The list would then be presented to the Scottish Cancer Registry to search for any cancers subsequently diagnosed.

This would provide a more secure basis for measuring the age-specific incidence of breast cancer among women referred to the "family history clinics" in Scotland but judged to be at "low" (i.e. "below threshold") genetic risk and excluded from any regular surveillance programme.

This particular section of my thesis may not give immediate answers but hopefully will provide enough information to allow continuing studies to look into the accuracy of threshold setting for true "low risk" women for whom regular surveillance at an early age is not justified.

As the 2004 NICE guidelines recognise, the raw data on which current thresholds have been set are insubstantial and validation is urgently needed.[39]

From 1994, all four Scottish centres used guidelines created by the Scottish Office Home and Health Department which were incorporated into the Scottish Intercollegiate Guidelines Network in 1998[38,72] (see Table 2.1, page 21). This was therefore the starting date for the survey.

NICE guidelines set a different threshold from the Scottish guidelines by the removal of any age restriction in the case of just two affected relatives with breast cancer. Under "NICE" this would be sufficient for classification as "moderate" genetic risk, whereas SIGN (and most other guidelines published up to 2004) required that both relatives must have been diagnosed before age 60 years.

The term "NICE moderate" is used hereafter to describe the subgroup of women who would have been at "moderate risk" under NICE guidelines but were treated as "low risk" under SIGN guidelines.

Records of all 4 Scottish "breast cancer family history clinics" were examined to identify all women referred to the clinics from the period between January 1994 and December 2003 who had been placed in the "low risk" category after assessment of the family history and for whom follow up was not arranged (according to SIGN guidelines that time).

We then asked the Scottish Cancer Registry to inform us whether any of the women identified as "low" risk were subsequently diagnosed with cancer. Special attention was given to breast and/or ovarian cancers. Permission from the Privacy Committee of the Scottish Cancer Registry was sought and granted for this information to be collected. The Registry records were complete to the end of 2002 and 90% complete for 2003 at the time of the study.

Confirmation and further clinical and pathological details of the breast and/or ovarian cancer cases identified through the Cancer Registry were sought through full check of the surgical and pathological findings in the individuals' case notes.

We calculated the period that elapsed between discharge from the clinic and December 2003 for each woman referred. From that, and the date of birth, it was possible to calculate the number of years spent in each five-year span (35–39 years, 40–44 years and so on) between discharge and December 2003. These were aggregated to give the total number of woman years of observation.

Corresponding "expected" numbers of breast cancer cases were then derived from the Scottish Cancer Registry figures.[212]

We identified 2074 women in total who met the criteria required ("low" genetic breast cancer risk). They had been followed up for an average period of 4 years and complete data were available for 98% of them. For the remaining 2%, some data (e.g. post code or exact date of clinic discharge) were missing but sufficient information was recorded to include them in the overall analysis.

From January 1994 to December 2003, 28 invasive breast cancers in 26 women from all the Scottish centres were diagnosed among patients not considered to be at significantly increased familial risk for the disease. Two patients with simultaneous bilateral breast cancers were counted as two cases each (both of these women were aged just 50 years at their diagnosis).

At least one of them now belongs to a "high risk" category as two further early onset breast cancer cases have subsequently been detected in close relatives.

The expected number of cancers was 14.4, giving a relative risk of 1.94 assuming that the cancer ascertainment was complete. This is a conservative assumption because the Scottish Cancer Registry can never be 100% complete and, for example, would have no record of cancers diagnosed outside Scotland. The figure is considerably higher than the relative risk threshold set by the currently available guidelines of 1.7.

NICE guidelines define women at "moderate risk" for breast cancer as those with a risk of 3–8% between age 40 and 50 years or a lifetime risk of 17% or greater, but less than 30%. For the "high risk" category, the risk before age 50 years must be greater than 8% and lifetime risk greater than 30%. Women at high risk will have an approximate chance of 20% or greater of carrying a mutation in one of the major genes implicated in familial breast cancer.

The guidelines classify "low risk" as being at near population risk, that is a risk of less than 3% between age 40 and 50 years and a lifetime risk of less than 17%.

In theory they should be dealt with in the primary care setting.

When NICE criteria were applied to our series, nine of the 28 cancers diagnosed before the end of 2003 were in women with a "moderate risk" classification. If those women are excluded from the analysis, the overall relative risk falls to 1.32.

Table 6.1 summarises the findings of this study where data on 28 breast cancers were recorded among 2074 women discharged from breast cancer family history clinics in Scotland during the period of January 1994 to December 2003.

Table 6.1: Summary of the study findings on the incidence of breast cancer in "low risk" women discharged from regular surveillance programmes.

Age range	Women-years of F/U	Breast Ca expected (population data)	Breast Ca recorded	
			Total cohort	Exluding "NICE moderate" cases
<35	843	0.25	0	0
35–39	1341	0.8	1	1
40–44	1552	1.9	2	1
45–49	1522	2.7	4	3
50–54	1405	3.9	11	8
55–59	846	2.5	5	5
60–64	454	1.4	2	0
65+	320	0.95	3	1
TOTAL	8283	14.4	28	19

Of the 28 breast cancers recorded in the total cohort, 18 were screen detected and 10 were symptomatic. The cancer types were as in Table 6.2.

Table 6.2: Findings from the survey of "low risk" women breast cancer diagnosis (according to pathological findings)

	Node-negative	Node-positive
Invasive ductal carcinoma	13	6
Invasive lobular carcinoma	2	1
Invasive tubular carcinoma	4	0
Mixed types	2	0
TOTAL	21	7

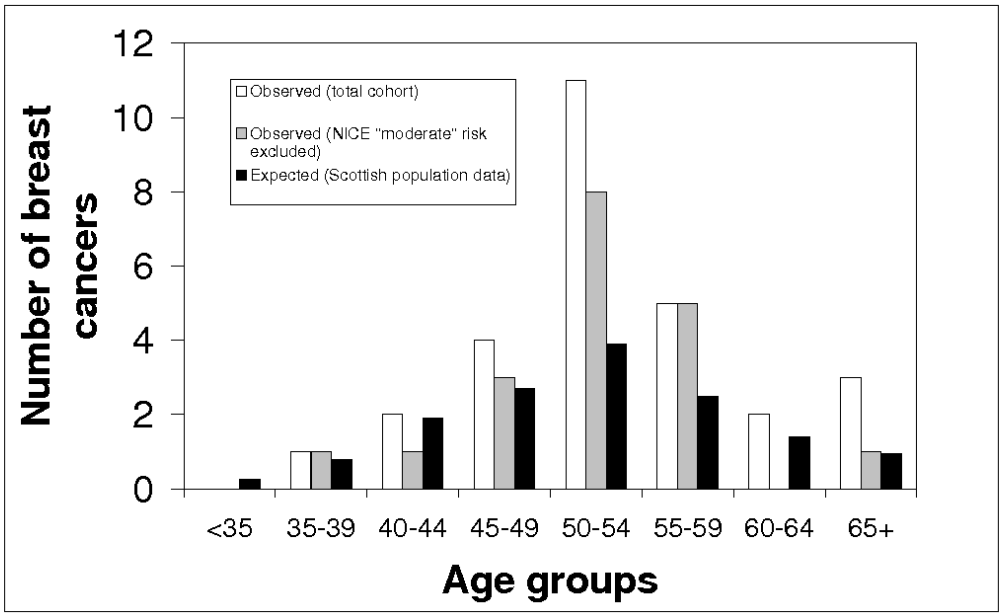

Figure 6.1: Observed and expected breast cancer cases in "low" risk women seen through the family history clinics across Scotland (1994–2003)

The incidence of breast cancer in "low risk" women in Scotland over the period age 1994–2003 is shown in Figure 6.1. A further nine invasive cancers were recorded since December 2003 (Figures 6.2 and 6.3), but since data for the latest period (2004/2005) are very incomplete, these have not been included in calculations of relative risk. They can, however, be included in evaluating the age-distribution of cancers and family histories of those affected.

The age group between 45–59 seems to be the most important for the questions raised on the "low" risk threshold as they constituted some 46% of our total cohort but generated 71% of the breast cancers (84% if the NICE "moderate" subgroup are excluded). The relative risk level was the highest in this group when compared with the other groups in the study (2.2 if the NICE "moderate" cases are included, 1.8 if not).

In fact, all but two of the 20 cancers in this age group were diagnosed by age 56 years and one more at 57 years.

Between the ages of 45 and 55 years, the risk for women with a "weak" family history of breast cancer does appear to be higher than that seen in the normal population and at a level greater than the predictions on which current guidelines are based.

Given that the large peak of cancers occurring in the 50–54 years of age group is accounted for by cases diagnosed at first NBSP mammographic screen (6 aged 50 years, 2 aged 51 years and one at age of 52 years) there is a strong suggestion that more regular screening would lead to earlier diagnosis in these "low risk" women.

By the same argument, most of those recorded as presenting in the 55–59 years age group might have been detected by regular screening up to the age of 55 years since almost all were actually diagnosed by age 56 years.

Hence there could be a case for review of the criteria for regular surveillance in the 45–55 years age group.

All the tumours discussed so far were invasive breast cancers. Two thirds were detected by clinical and/or mammographic examination, (through the National Breast Screening Programme in most of the cases).

Other relevant cancers for our study included: three DCIS (ductal carcinoma in situ) cases; one woman was found to have an unexpected second focus of invasive disease in her mastectomy specimen after surgery (not scored here as a separate cancer), three epithelial ovarian cancer cases (serous, endometrioid and mucinous types respectively). A single case of ovarian borderline tumour was also identified.

With the changes made in the multidisciplinary clinics (Edinburgh and Dundee), since 2004, women found to be at "low" genetic risk for breast cancer no longer attend the clinics and therefore do not have clinical examination nor a mammogram before being discharged.

Of the total number of cancers (36) detected (including the ones from January 2004), 12 would, under the most recent guidelines of NICE, have had their familial risk classified as "moderate " rather than "low", as per SIGN guidelines (see Figure 6.3).

Re-examination of the family history background of 400 from the total number of patients in this particular study suggests that less than 10% of them would in fact

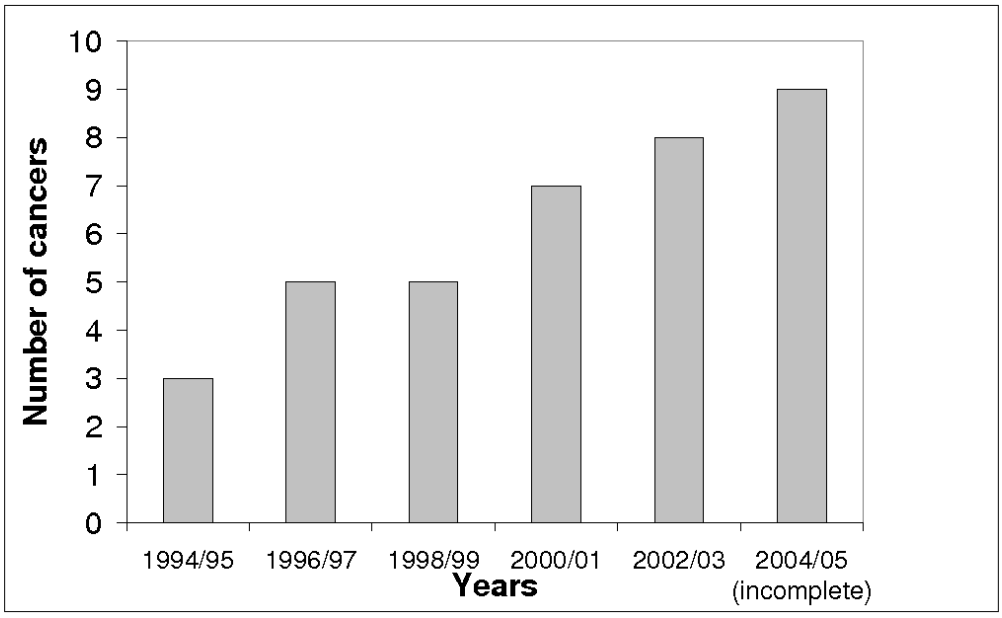

Figure 6.2: Breast cancers detected by year of diagnosis in "low risk" women across Scotland during study period

be reclassified as "moderate" risk if the NICE criteria were used. "NICE moderate" women are therefore substantially over-represented among those who developed breast cancer.

The findings suggest that the NICE criteria are more accurate in determining familial breast cancer risks than the ones used in Scotland (SIGN guidelines) or other widely used algorithms to quantify breast cancer risk, though all of them have substantial confidence intervals.[23,24,36]

In the group of "NICE moderate" women affected with breast cancer, half of them were over 60 years of age. As breast cancer is an age-related condition, there could be an increased number of breast cancer cases in those women and among their (older) relatives but not necessarily indicating an increased genetic risk for the disease.

Only three cancers in total were recorded before age 45 years and this represents no excess over expected numbers. These observations further support the

concept that the age group 45–55 years is the one on which we should concentrate in judging the provision that should be made for women with a "limited" family history of breast cancer.

This age group should receive special attention, as their risk up to the age of 56 years could be significantly higher than that of the normal population. They would perhaps benefit from regular surveillance starting at 45 years of age and continuing to age 55 or 56 years, possibly at 18 month intervals rather than annually and interdigitating with the NBSP from age 50 years.

The minority with a very strong family history, suggestive of a BRCA mutation will be at risk from a much earlier age and, as discussed in Chapter 5, require rather different service provision.

To my knowledge, this is the first serious study of how the various guidelines and risk assessment protocols actually work in practice. The group of women identified in our cohort should be followed up for longer period of time in order to establish whether any further modifications would be necessary to the guidelines. This would contribute to the urgent requirement identified in the 2004 NICE report, for proper validation of risk assessment models used in familial breast cancer genetics clinics.

Interestingly, hardly any of the women diagnosed with cancer reported this back to the breast cancer family history clinics although, in most instances, the new cancer case changed the risk for close relatives to "moderate". This is a cause for concern because, at their discharge discussion with the genetics associate and in the explanatory letter from the clinic, they had been advised to inform the genetics clinics of any change in their own symptoms or their family history.

Preliminary findings for the years 2004 and 2005 are in keeping with the excess risk observed. It will be very important to follow this cohort for at least further few years so a more accurate analysis of the true incidence can be performed to generate a substantial evidence base to allow further modifications to the guidelines for the familial breast cancer services.

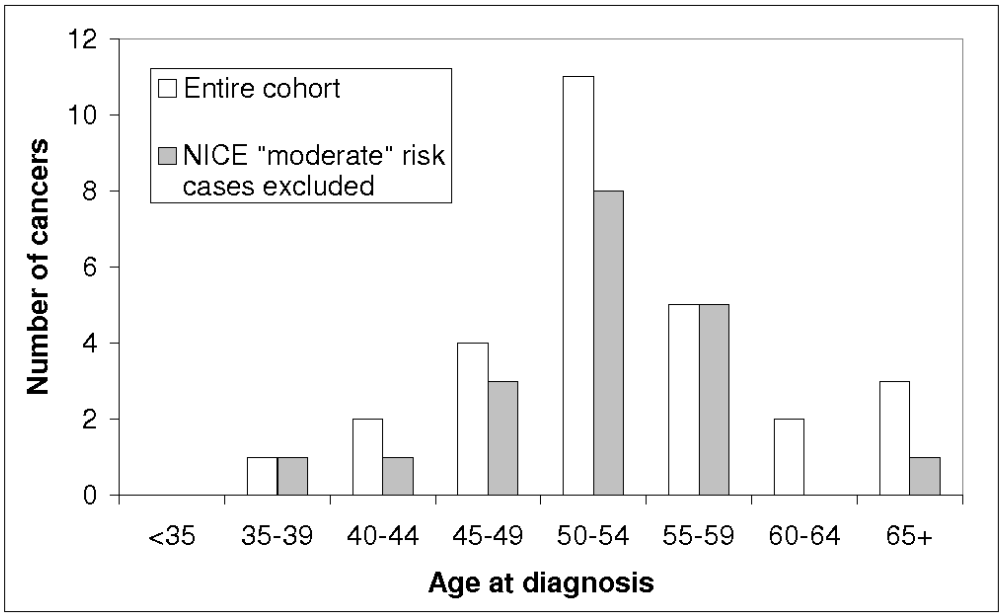

Figure 6.3: Number of breast cancers detected in "low risk" women by the age at diagnosis (all cases 1994–2005 included)

6.1 Conclusions

Given the haste which the guidelines were drawn up in response to the demand for breast cancer family services, it would have been unreasonable to expect the threshold setting to have been absolutely correct. By taking a minimal risk of 1.7 times the population risk level, it was anticipated that the incidence of breast cancers in a population enrolled in special screening programmes would approach 6 per 1000 examinations, (the same as the National Breast Screening Programme for older women) and as I have shown in Chapter 4, this expectation has been fulfilled.

Nevertheless, I have demonstrated that at least one subgroup of women currently excluded from surveillance by the SIGN guidelines (1998) threshold criteria ought to be included, these are women with 2 affected close relatives at least one of whom was aged 60 years or older at diagnosis.

6.2 Future work

The Scottish "low risk" cohort needs to be studied in greater detail and for a longer period to identify further modifications to the threshold setting. Collaboration with the Scottish centres, Cancer Registry-ISD, genealogy service and Registrar General should continue to enable data collection for analysis. We are looking into the development of a UK-wide collaboration following this group of women, however there may be some difficulties elsewhere in the UK as those registry and central records services may not be as fully functional as in Scotland. Unfortunately a European-wide collaborative study will also prove difficult, owing to the diversity of clinic settings and availability of supporting services.

Chapter 7

Costs and cost-effectiveness issues

This chapter deals with just one question but it is the central issue of the whole thesis:

Is current management of women at increased familial risk of breast cancer cost-effective?

That can be broken down into a number of elements:

1. What are the cost associated with current practice?
2. What are the benefits?
3. Can potential changes in practice be identified that may reduce costs, increase benefits or both?

The terms "cost" and "benefits", of course, are not restricted to monetary definitions. They also encompass patient experiences, anxieties and their resolution. These latter elements may be more difficult to quantify but, as far as possible I have taken them into account.

7.1 Background and methods to obtain cost figures and their accuracy

For those with a family history of breast cancer their lifetime risk of developing breast cancer may be substantially increased and as at least some forms of hereditary breast cancer tend to occur at young age of onset, it is generally accepted

that the NBSP (National Breast Screening Programme), available from the age of 50 years, provides insufficient protection. Debates about whether or not screening young women for breast cancer is beneficial are continuing.[114,122,213]

Health economics aims to evaluate any new healthcare intervention to obtain a full measure of its benefits and costs to society. There are very limited published data on the subject of cost-effectiveness of familial breast cancer management and such readily available information as exists on cost issues related to the treatment of breast cancer patients with new (and expensive) drugs and interventions is not completely up to date.[65,87,89,103,148]

Most of the published analyses relate to hypothetical models and only limited hard data have been used in the calculation of costs and effectiveness in the management of women with familial breast cancer risk.[1,90,91,151,214] There is, in my view, a danger in undertaking and publishing apparently detailed cost-effectiveness projections which lack a secure evidence base because they can be taken as authoritative and may have considerable influence on the commissioning of services (under insurance-based or publicly funded systems) yet ultimately prove misleading. A very clear example is the impressive report published this year in the Annals of Internal Medicine (the official journal of the American College of Medicine) entitled "Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation".[1] The authors "*applied a Markov process and used 25000 Monte Carlo simulations with TreeAge DATA Pro software to estimate the cost-effectiveness of [several different] preventive strategies*". Their findings are extraordinarily detailed but, for the purposes of their study, the authors "*assumed that BRCA1- or BRCA2- positive women who developed cancer would have the same conditional probability of death as women with cancer in the general population*". Further, they comment that "*Most other studies have not suggested that mortality is higher for mutation carriers than for other women with breast cancer. The higher the mortality assumed to be associated with BRCA1 or BRCA2 mutations given surveillance alone, the greater are the survival and cost-effectiveness benefits of preventive interventions. We used the most conservative estimates of each parameter so that our model would, if biased, favour surveillance over other preventive interventions*". Real data, as documented for example in Chapters 5 and 6 of this thesis, demonstrate that the assumptions underlying the study are incorrect. Carriers of BRCA1 mutations who develop breast cancer have very different risks of dying

from it, compared to BRCA2 mutation-carriers or women with a family history of the disease but no demonstrable mutation. The relative cost-effectiveness of surveillance or of prophylactic intervention for different categories of women at increased familial risk can only be assessed with real validity if these facts are accommodated in the calculations.

My own approach has been to measure the real (mainly modest) shifts in stage of breast cancer diagnosis achieved through screening and hence the modest gains in survival for those affected. Costs calculations were also based on real data gathered as described below.

I began by collating all clinic procedures for each woman attending. I have also identified all the Tayside cancer family service women in whom breast cancer was detected. From their case notes, I tabulated all the procedures performed, drugs used and in-patient stays for the duration of treatment.

Costs figures were calculated using available information published locally or nationally, the main sources being the report by my Tayside colleague Dr John Dewar[103] on costs of breast cancer management and unit costs derived from the Scottish Health Statistics on breast cancer - ISD Scotland (blue book). For further details I contacted Mr Derek Colley, Mr Glen Finnie from the Finance Department at Ninewells Hospital, Mr David Carson Head of Financial Performance Management for NHS Tayside.

Because of the different outcome from screening (detailed in Chapter 5), BRCA1 mutation carriers were treated as a special group, for whom prophylactic surgery should be considered as a preferred management option.

I have not been directly involved, as yet, in formal studies of patients' psychological reactions to risk assessment, screening or other aspects of management, apart from those reported in Chapter 4. However, reference is made to the relevant literature wherever appropriate.

7.2 Basis of calculations

The survival benefit of detecting breast cancer at an early rather than at an advanced stage for a "typical" breast cancer patient was the principal base for cal-

culation of cost-effectiveness of surveillance (see Chapter 1 for an introduction to the staging and current management of breast cancer).

I have used the term "typical" breast cancer patient as a hypothetical individual, though, in reality, no such "typical" breast cancer patient exits. Nevertheless, I believe the composite pictures upon which my calculations are based, are realistic and derived from the observations in the Tayside clinic, across Scotland and through multi-national European collaborative programmes described in the preceding chapters.

The following assumptions, all supported by the findings discussed in preceding chapters and in most recent UK standard reviews of clinical aspects of breast cancer[215,216] are made in order to generate the figures from which costs and benefits are finally calculated:

1. Within a "breast cancer family" surveillance programme, breast cancers are detected at a rate of six per thousand annual examinations.

2. Seventy-seven percent of the breast cancers detected among women in such a surveillance programme are "early stage" and node negative.

3. Fifty-five percent of cancers detected among young women (<50 years) who have NOT been enrolled in any screening programme are "early stage" and node negative. This means that surveillance increases the proportion of "early" cancers by 22%.

4. "Early" node-negative breast cancers have a 70% prospect of complete eradication ("cure") by primary surgery, radiotherapy and, where appropriate, adjuvant chemotherapy.

5. "Late", node-positive breast cancers have only a 30% prospect of complete eradication ("cure") by primary surgery, radiotherapy and adjuvant chemotherapy.

6. Those not "cured" by their primary treatment (30% of "early" cases, 70% of "late" node-positive cases) will require additional treatment and investigations, often involving expensive drugs such as taxanes and/or Herceptin and are likely ultimately to require palliative care.

7. The quality of life (after primary treatment) for "cured" patients is excellent and, since we are dealing mainly with women around age 50 years, "cure" of breast cancer provides a further 25 years of life (25 QALYs).

Combining the stage at diagnosis, the cost of specific element of treatment and the proportion of patients requiring each element, generates Table 7.1.

Table 7.1: Costs for "typical" pre-menopausal women that developed breast cancer: two distinct scenarios are presented, "early" stage at presentation (70% anticipated cure) and "late" stage (70% anticipated recurrence with ultimate treatment failure)

	Late stage (T3/T4 N+)		Early stage (T1/T2 N−)	
Anticipated "cure" rate >10 years (i.e. disease-free survival)	30%		70%	
	%	Cost	%	Cost
Initial inpatient stay (average five nights @ £449), £2245	85	£1,908	100	£2,245
WLE + ax. surgery, £1,673	15	£251	60	£1,004
Mx + ax. surgery, £2,421	70	£1,695	0	£0
Mx + ax. surgery + reconstr., £4,513	0	£0	40	£1,805
Anthracyclines × 6, £1,836	50	£918	60	£1,102
FEC × 6, £3,155	50	£1577	0	£0
Taxanes, £9,160	70	£6,412	15	£1,374
Herceptin (2yr), £44,000	25	11,000	5	£2,200
Bisphosphonates (2yr), £4,000	50	2,000	10	£400
Tamoxifen (5yr), £43	50	£21	50	£21
Radiotherapy (standard), £1,500	100	£1,500	60	£900
Palliative radiotherapy, £400	70	£280	15	£60
Palliative care inpatient stay (15 nights @ £3439), £51,585	70	£36,110	25	£12,896
TOTAL cost		£63,672		£24,007

(WLE = wide local excision; ax. surgery = axillary surgery; Mx = total mastectomy; reconst = breast reconstruction; FEC = chemotherapy regime using 5-fluorouracil, epirubicin and cyclophosphamide). Note that, in deriving the total treatment cost for each category of "typical" patient, allowance is made for the proportion within each category that will actually require any given component of the treatment options. Cost figures are derived from reference[103] and sources cited in text.

The figures for "early stage" cancers include around 15% of cases of DCIS on the grounds that detection at this "pre-cancerous" stage will prevent later de-

velopment of invasive cancer, which is, of course an important purpose of the screening programme.[182]

For each woman with breast cancer diagnosed in stage 1 or 2, rather than stage 3 or 4, there is, from the calculations, an average saving in *direct* healthcare costs of £39,665 (£63,672 − £24,007).The additional costs for late stage patients are accounted for by more extensive initial surgery, greater requirement for costly "second line" chemotherapy and particularly by the cost of palliative care in the last year of life. This last figure may seem surprising but palliative care requires a high staff/patient ratio and expensive accommodation and facilities. For comparison, the 2004 figures from the Kaiser Permanent Health Care Organisation in the USA[1] are shown in Table 7.2. "Acute care" costs – i.e. initial surgery, radiotherapy and chemotherapy are higher than I have estimated for Tayside and palliative care is cheaper but still much the most expensive element of the "package". Figures from two Canadian studies were given in Chapter 2; though some years out of date now, their findings are broadly in line with the above.[95,96]

Table 7.2: Representative costs of management options for familial breast cancer in North America (quoted in[1]). Conversion £1 = 1.8 US$

Treatment element	Cost (converted to £ sterling)
Primary surgery, radiotherapy and chemotherapy (with in-patient stay)	£14,670
Yearly costs thereafter	£3,770
Palliative care in last year of life	£21,630
Prophylactic mastectomy	£6,280
Prophylactic salpingo-oophorectomy	£2,570

From the costs calculations in Jane Kenyon's study (Chapter 5), which I supervised, patients with nodal involvement were more expensive to treat with a mean cost of £7,423.7 when compared to £5,836.4 for node negative patients.

However, very few of the patients in that study had reached the terminal care stage and drugs such as taxanes and Herceptin were not yet available (chemotherapy regimes then in use were based on CMF and anthracyclines). Therefore the full cost implication for the NHS cannot be derived directly from that study.

We have found that surveillance increases the proportion of "early stage" breast cancer diagnosis from 55% to 77% (tables 5.2 and 5.3). Thus, for every hundred

breast cancers arising in women enrolled in an annual screening programme, 22 are "transferred" from the poor to the good prognosis category and hence, in cost terms, from the left to the right hand column of Table 7.1, with a total saving in direct healthcare costs of £872,630 (22 $\times$ £39,665).

The detection rate for breast cancer in a cancer family service surveillance programme has been estimated at 8 per thousand screening examinations.[98] The figure for Tayside has been about 5.8 per thousand, though this is likely to increase as more stringent criteria are applied for entry to the programme.

Therefore, taking 6 per thousand as a realistic figure, the shift to earlier stage at diagnosis would affect 1.32 women per thousand screens (22% of 6), with a saving of £51,358 in NHS costs (1.32 $\times$ £39,665).

Coincidentally, the Tayside service now undertakes about one thousand screens per year and, as recorded in Chapter 4, the NHS cost is just over £100 per screen. Hence, the net annual cost of the Tayside programme is around £100,000, less the savings (calculated above) of £51,358 – i.e. £48,642.

If each woman shifted from "late" to "early" stage diagnosis through screening improves her prospect of long-term survival ("cure") by 40% (from 30% to 70%) and cure adds 25 years of high quality of life (25 QALYs), the gain is 13.2 QALYs per year (25 $\times$ 0.4 $\times$ 1.32) at a cost of £3685 per QALY (£48,642 $\div$ 13.2).

This does not take into account the fact that many women in their 40's and 50's years are in productive employment and/or undertaking important family responsibilities which have an economic value. In practice, therefore, the net cost to the national exchequer per QALY gained is likely to be much less than £4,000.

I have arrived at a much lower cost per life-year gained than was calculated in the pilot study by Kenyon.[217] She reported a figure of £19,619 per life-year gained by screening young women at increased risk of developing breast cancer.

However, as noted above, in that small study, the five-year time-span was a limiting factor and the true cost of follow-up, treatment for recurrent problems and palliative care was not included. Her calculations were based largely on the costs of primary surgery, radiotherapy and chemotherapy which, as shown in table 7.1, do not differ greatly for the "early" or "late" stage cases.

As discussed in Chapter 2, Heimdal and colleagues[148] calculated the costs of diagnosing familial breast cancer in Norway using empirical figures from the

Norwegian Health Insurance system and the cost per year gained was estimated at 753 Euros. This could increase to 832 Euros if a new strategy was implemented for identifying all "high risk" family by testing for genetic founder mutations in a Norwegian population. They also concluded that "inherited breast cancer could be cured for the cost of 750–1,600 Euros per each year gained".

Why our figures differ is explained in the following few lines:

Their costs, based on Norwegian health insurance charges, were lower (110 Euros per screen). Translating those figures in to pounds gave a cost of £78.50 per screen (110 Euros ÷ 1.4).

They assumed a 75% "cure" rate for cancers diagnosed in the screening programme and a gain of 30 years of life for each woman so diagnosed, attributing all of this to the screening programme – i.e. assuming 100% mortality if no screening.

Their breast cancer detection rate was very high because they concentrated on families bearing Norwegian "founder" mutations in BRCA1.

In our own calculations, we have allowed for the fact that some 30% of the "early stage" screen-detected breast cancers in young women will ultimately recur and prove fatal, whereas around 30% of the "later stage" cancers (typically those presenting in women not enrolled in a surveillance programme) are "cured" by primary treatment.

In addition, some non-screened cancers (55%) present at an early stage while some detected in a surveillance programme (23%) are already node positive.

The more recent study by Gui et al. (2006)[218] from the Royal Marsden Hospital, though based on a shorter time interval (16 months) and only 1132 patients, produced results comparable to our own. Only 2 out of 13 breast cancers diagnosed in their cancer family clinic had nodal involvement and over 85% of the cancers were diagnosed at screening mammography.

Realistically, therefore, any surveillance programme will have much less than 100% efficiency in transforming "fatal" breast cancer into the "curable" category. Despite this, our figures show that the cost per QALY gained is modest compared with many other interventions (e.g. coronary artery by-pass surgery, renal transplantation).[219,220]

7.3 Sensitivity analysis

Our calculations are particularly sensitive to changes in two specific parameters, namely the rate of detection of breast cancers in a surveillance programme and the effectiveness of screening in terms of shifting diagnosed breast cancers on average towards an earlier stage. For both, we have used values that correspond closely to what we have actually observed; however if, for example, the breast cancer detection rate falls to 4 per 1000 screens, while the shift to a curable stage at diagnosis remains at 22%, then the cost saving of £39,665 will be achieved for only 0.88 women per year (rather than 1.32), i.e. an annual saving of £34,905. The cost of screening 1000 women per year is fixed at £100,000 so the net cost (£100,000 − £34,905) becomes £65,095 and if each woman shifted to the "curable" category still gains 40% of 25 years (i.e. 10 years) of high quality life, 8.8 QALYs are gained each year, at a cost of £7396 per QALY.

Conversely, if the cancer detection rate rises to 9 per year (as suggested by Kerlikowske and colleagues in 1995[127]), then the saving rises to £78,537 (1.98 × £39,665) and the net annual cost falls to £21,465 (£100000 − £78,537) for a gain of 19.8 QALYs, reducing the cost per QALY to £1084.

If the shift to earlier stage at diagnosis of breast cancer applies to 15% of cancers rather than 22%, then the saving per 100 cancers detected reduces from £872,630 to £594,975 (15 × £39,665) and if the detection rate remains at 6 per year, the annual saving becomes £35,669 (0.9 × £39,665), set against a fixed annual cost of £100,000, giving a net annual cost of £64,301 for a gain of 9 QALYs, costing therefore £7145 per QALY.

Raising the proportion of patients whose cancers are detected at a significantly earlier stage from 22% to 30% has the opposite effect. The saving per 100 cancers becomes £1,189,950 (30 × £39,665) so the saving per year (if 6 cancers are diagnosed) is £71,398 (1.8 × £39,665) and the net cost per year reduces to £28,601 (£100,000 − £71,398) for a gain of 18 QALYs. Each QALY gained then costs only £1589.

Realistically, the number of cancers detected per year is likely to rise above the current level, rather than to fall, as more stringent procedures are applied for selection of those eligible to enter surveillance programmes (see Chapter 4). On the other hand, the proportion of breast cancer patients who benefit

directly from earlier diagnosis through screening may actually be lower than the 22% we have measured if, as discussed earlier, some of the apparent benefit derives from intrinsic biological differences between familial (non-BRCA-associated) and sporadic tumours.

Variations in these parameters can be combined, as illustrated in Table 7.3.

Table 7.3: Effects of changing sensitive parameters (numbers of breast cancers detected per year and percentage of patients who benefit from "stage shift" of their cancer) on cost effectiveness of surveillance programme for familial breast cancer

Breast cancers detected / yr	% shift to "curable" stage	Br Ca pts. benefitting per year	QALYs gained*	Annual saving £**	Annual net cost £***	Cost per QALY £
6	22	1.32	13.2	51,358	48,642	3685
4	22	0.88	18.8	34,905	65,905	7396
9	22	1.98	19.8	78,537	21,463	1084
6	15	0.9	9	35,669	64,301	7145
6	30	1.8	18	71,398	28,601	1589
4	15	0.6	6	23,799	76,201	12,700
4	30	1.2	12	47,598	52,402	4367
9	15	1.35	13.5	53,548	46,452	3433
9	30	2.7	27	107,096	−7096	−263

*Assumes 10 QALYs per additional patient detected at "early" stage (25×0.4). ** Assumes saving of £39,665 per additional patient detected at "curable" stage (from Table 7.1). *** Assumes fixed annual screening cost of £100,000 (for 1000 women screened).

Table 7.3 shows that, under the most favourable assumptions (9 breast cancers detected per year and 30% of these shifting from adverse to good prognosis as a result of surveillance) the savings actually exceed screening costs so that each QALY gained saves the NHS around £250. At the other extreme, if only 4 cancers are detected each year and just 15% of these benefit from diagnosis at an earlier stage (compared with no screening) then each QALY gained could cost over £12500.

7.4 Carriers of BRCA mutations

The foregoing discussion applies to the cancer family clinic population in general, the great majority of whom do not carry BRCA1 or BRCA2 mutations. The

minority (about 5%) who carry BRCA1 mutations represent a special case. Even when diagnosed early, breast cancers in this group carry a very bad prognosis and prophylactic surgery is a serious option for them.

At present, around 12% of breast cancers diagnosed among the Tayside breast cancer family clinic population (5 out of 42 cases since 1995) are known BRCA1 mutation carriers. This percentage may increase in the future as mutation detection becomes more efficient and as more efforts are directed towards known mutation carrier positive families.

The costs of treatment for a BRCA1 mutation-positive breast cancer are comparable to those shown for "late stage" cancers in table 7.1 i.e. long-term survival with conventional treatment is about 30%.

At present, we see no evidence that screening will achieve a shift in survival prospects for them. The question then is how cost-effective is prophylactic surgery for this group?

Table 7.4 shows current costs for women undergoing risk-reducing surgery assuming all patients who have prophylactic mastectomy (+/- reconstruction) also have bilateral salpingo-oophorectomy (BSO) as a separate procedure.

Table 7.4: Cost of prophylactic surgical intervention for BRCA1 mutation carriers.

Procedures	Cost
Bilateral salpingo-oophorectomy (BSO)*	£1,500
In-patient stay (av. 3 nights @ £449)	£1,347
Bilateral mastectomy	£2,421
In-patient stay (av. 5 nights @ £449)	£2,245
TOTAL (BSO and mastectomy)	£7,513
Bilateral mastectomy and reconstruction (TRAM flap)	£4,513
In-patient stay (average 8 nights @ £449)	£3,592
TOTAL (BSO + Mx + TRAM)	£10,952

(TRAM flap = transverse rectus abdominus myocutaneous flap reconstruction)
*Assuming all patients who have prophylactic mastectomy (+/- reconstruction) also have BSO (as a separate procedure). Cost figures derived from reference[103] and sources cited in text.

7.5 Savings (direct health care) from prophylactic surgery

For one BRCA1 mutation carrier (who has 80% lifetime risk of cancer and a 70% risk of death from breast cancer if it should occur), the risk of death from cancer is reduced by oophorectomy from 56% to 28% as risk tends to be reduced by half. The risk of death from cancer is reduced by mastectomy plus bilateral salpingo-oophorectomy (BSO) from 56% to 5%.

Therefore, applying the figures from tables 7.1 and 7.4, the direct healthcare cost of each BRCA1 mutation carrier who does not have prophylactic surgery is 56% of £63,672 plus 24% of £24,007, i.e. £41,418. This is reduced by half through BSO and by 95% if BSO is combined with bilateral mastectomy.

Hence, BSO at a cost of £4,850, saves £20,709 per patient, while combined prophylactic mastectomy and BSO, at a cost of £7,961, saves £39,347 per patient.

These figures apply to BRCA1 mutation carries only (around 5% of clinic population at present) but given the very high lifetime risk of breast and/or ovarian cancers, the savings apply to almost all of these (in contrast to the situation for non-BRCA1 mutation carriers, only a minority of whom will actually develop cancer).

Years of life gained by prophylactic surgery for BRCA1 mutation-positive women are around 25 years. Therefore prophylactic surgery is highly cost-effective in this group.

Limited studies on psychological consequences of prophylactic oophorectomy and mastectomy suggest that the impact is usually manageble[221,222] but this is an area that requires much more work.

The psychological price of annual screening, with its attendant reminder of risk for breast cancer and the anxiety level acccompanying the wait for the results of screening applies to all women attending a "family history" surveillance programme. It is difficult to quantify this cost accurately, however, recent reviews demonstrate that the impact on general anxiety or cancer-specific worry is broadly neutral.[223,224] It is clear that women aware of their possible increased risk for breast cancer strongly favour entry into regular surveillance programmes with

mammography screening, regarding its availability as providing peace of mind and comfort rather than a source of anxiety.[187,189]

7.6 Conclusions

I have arrived at estimates of the net economic cost of management for women in different categories of familial risk of breast cancer. While there is clearly some margin of error around the estimates, I believe they are the most robust currently available.

For the great majority of women eligible for inclusion is special surveillance programmes, the net cost per QALY falls within the range £-263 to £12,700, with a median value of £3685. Even the highest of these estimates lies within the limit considered acceptable by NICE.[225]

For women who carry a pathogenic mutation in BRCA1 gene, screening, as currently practiced, does not provide adequate protection but prophylactic surgery is plainly cost-effective. New diagnostic procedures, such as MRI, may change the situation but several years of follow-up of MRI-detected breast cancers in this subgroup will be required to verify or refute this. A most important outcome of the studies reported in this thesis is recognition that management needs to be tailored to the nature of the genetic risk i.e. it should be different for BRCA1 mutation-carriers compared to BRCA2 mutation-carriers or those with no mutation in either gene.

Of course there are some remaining issues, such as the residual risk of developing primary peritoneal carcinoma and of other BRCA1 associated cancers (1–2%) after undergoing risk-reducing surgery.

Other genes are yet to be found and new data will no doubt emerge, leading to further recommendations for both the treatment of hereditary breast cancer and prophylactic interventions in their relatives seeking advice about their risks for breast cancer.

At the moment, the best intervention available for those women at high risk either of developing a first breast cancer or of developing a second breast cancer, after initial treatment, is prophylactic surgery.

It is to be hoped, therefore, that with new evidence available on the outcomes of women with a genetic mutation for breast and/or ovarian cancers the uptake for prophylactic interventions in those women will improve.

Chapter 8

Conclusions and recommendations

Since the start of the 20th century, breast cancer management has seen major transformation affecting diagnosis and treatment. More recently, emerging information on the genetic basis of the disease has given unprecedented potential power for the identification of those at increased risk and opportunities for regular surveillance and prophylactic risk-reducing measures.

Developments in several medical fields have contributed to those changes, particularly with the discovery of genes responsible for breast cancer and applied research for the evolving new era in medicine: the genetic revolution.

Unfortunately, cancer genetics services were not considered until recently as part of routine healthcare provision, but have evolved mostly as part of research programmes. Eventually, knowledge of the genetic implications of given conditions (partly via the creation of advocacy groups) has prompted changes in the consumer-client led world.

Changes in policy-making processes in health care have meant that comprehensive genetic services for the population are beginning to evolve. Among these are the design and implementation of guidelines for women at significant inherited risk for breast cancer.

Proper assessment of genetic risks in the management of familial cancer allows healthcare resources to be used in the best possible way in this country, targeting the individuals that are most likely to benefit from these services. Similar "guidelines" approaches are emerging worldwide.

8.1 Summary of the work recorded in previous chapters

Risk assessment

It is, of course, necessary in order to achieve the aim of maximising cost-effectiveness, to have accurate risk assessment of the individuals seeking advice.

Scotland is privileged in maintaining excellent and comprehensive Cancer Registry services as well as public records of births marriages and deaths. Access to those services puts our cancer genetics clinics in a particularly strong position to extend and verify self-reported family histories of breast and ovarian cancers as well as other heritable malignancies.

Communication of "low genetic risk" assessments

The communication of risk outcome to those individuals considered to be at "low genetic risk" by letter is acceptable; face-to-face interview only seldom adds relevant information to what has already been collected through standardised Family History forms received at an early stage of the risk assessment process.

Identification of "low genetic risk" and communicating this assessment without the need for a clinic appointment could reduce direct cost to the NHS by at least £100 per woman per year.

Co-operation

A truly effective cancer genetics service requires close co-operation between primary care team, family members and the staff of the genetic service itself. This is a more practical approach than allocating "gatekeeper" responsibility to GPs who lack the time or facilities to fulfil that role and who are (rightly) reluctant to adopt it.

As we have demonstrated, the percentage of "low risk" referrals increases considerably when all appropriate resources (including use of a Cancer Registry

–based medical genealogy service) are applied to the process of verification of information provided in the family history form.

If the triage system, evaluated in this study, for selection of women at increased risk for breast cancer is adopted as routine, no net increase in NHS resources for familial cancers will be entailed.

It remains to be seen, however, to what extent the same policy could be implemented in the UK regions that do not have comparable access to Cancer Registry and genealogical data.

For the women who fail to return their family history questionnaire (and who may have real difficulties in doing so) further discussion between clinic specialists and primary care team is currently addressing their management.

Unfortunately, mammographic surveillance and clinical examination cannot be offered to those women who fall in the "lower risk" category. It is inevitable that this generates disappointment. For those advised of a "low risk" assessment but who remains anxious about the issue of cancer risk, something more than a simple letter of reassurance may be required and this is also on the agenda for discussion with the primary care teams.

Implementation of NICE recommendations

As presented in Chapter 6, there is some indication that cancers could be missed if all women categorised by current guidelines as "below threshold" level of risk are excluded from surveillance programmes.

Our immediate conclusion is that the NICE recommendations should be implemented in Scotland – meaning that women with two close relatives diagnosed with breast cancer *at any age* should be classified as "moderate risk".

In the longer term, further studies are required to look into any other modification of criteria for entry to surveillance programmes – for example, whether a subgroup of women with relatively "weak" family histories of breast cancer should nevertheless be offered some extra screening, say from age 45 to 55 years. Dietary and lifestile intervention studies could play a role in this group.

Continued follow up of the "lower risk" cohort described in this thesis should contribute to resolution of this question but work is justified on a wider scale

and it is to be hoped that other centres may be able to replicate or extend our study.

Cost-effectiveness of surveillance and prophylaxis

Overall measures of cost-effectiveness of the services provided for familial breast cancer are difficult because it takes time to gather and interpret the real data required to make sound judgements. It is perhaps unfortunate that a number of seemingly authoritative statements and recommendations have been published over the years based on false assumptions—for example, that all categories of familial breast cancer fare equally well (or badly) under regular surveillance.

Estimates of the efficacy of surveillance or of prophylactic surgery appear sometimes to have been plucked from the ether. My attempts to derive true figures for cost-effectiveness (Chapter 7) are admittedly, approximations that may well have to be refined as more complete data become available but they do begin to show a coherent picture.

Regular surveillance for the great majority of women at increased familial risk of breast cancer (including those with BRCA2 mutations) is cost-effective, reducing mortality and morbidity at a median estimated cost of around £3,700 per QALY gained.

For the minority who carry mutations in BRCA1, however, screening is ineffective while prophylactic salpingo-oophorectomy, with or without total mastectomy, offer useful protection and are clearly cost-effective. How many lives are saved with such programmes and at what cost for the currently stretched resources within the National Health Service? Continuing prospective audit should ultimately answer these questions more authoritatively than the present study is able to.

Development of medical practice

As part of their professional role, clinical experts in genetics and surgeons involved in the care of women at genetic increased risk for breast/ovarian cancers must help policymakers to address the challenges encountered in this new

evolving area of medical practice, with continuing evaluation of the benefits and harms of delivering this service.

Guidelines must be refined to meet the increasing demands upon such services and attention must be given to education of all members of the healthcare team involved in the delivery of the service so that they can cope with the rapid changes in knowledge of the underlying genetics and implications for service provision.

We should ensure that all patients likely to benefit from this service provision have access to it in the future. The value of genetic testing depends on the power of measures in place to reduce risk for a given disease and/or to improve clinical outcomes.

It is now well recognised that screening programmes for women at genetically increased risk for breast cancer are effective in detecting most cases at an early ("curable") stage of the disease. This is also true for several other hereditary cancers such as MEN-2 and APC. However, it is not true for hereditary ovarian cancer and for some others, such as Gorlin's syndrome or MEN-1, it remains unproven.[226–228]

Providers of diagnostic genetics services have an obligation to disclose complete and up-to-date information on availability, acceptability and potential efficacy of the interventions on offer as many of the choices available will have significant impact on the lives of those required to make them.[229]

It is now possible to define more precisely the type of care needed for women who carry BRCA1 and/or 2 mutations, ranging from close surveillance to prophylactic surgical interventions,[49,61,229] making these options available to them with advice based on the best currently available evidence.

8.2 A return to the original questions

As a result of my studies I believe I can give answers, at least in part, to the questions set out in the Framework diagram in Figure 1.1.

Are current guidelines criteria of risk assessment valid? No, not entirely. The NICE guidelines which remove any age restriction when assigning risk to a history of two breast cancer-affected relatives appear to be more accurate than those

widely applied before 2004 but longer follow-up of the Scottish "lower risk" cohort may reveal a case for further adjustments that will provide some protection, through surveillance, for a group of women at substantially increased risk between the ages of 45 and 55 years.

Who should undertake risk estimation? This is very clearly a task for people with professional training in the field and with access to a supportive infrastructure. Genetics associates or Genetics Nurse specialists are very well placed for the purpose. Close two-way interaction with Primary Care staff should be recognised as an essential element of the risk assessment process.

How should discharge be managed for women referred to the service whose familial risk places them below the threshold for enrolment in a surveillance programme? It has emerged that their understanding of actual risk level is poor and that many believe they are at no increased risk at all, while others are dissatisfied with refusal to provide regular mammographic screening. Attention to improvement and standardisation of written information will be important but consideration must also be given to provision of face-to-face support, perhaps through professionally led group discussion sessions. Information from focus groups will be useful in developing these ideas.

How often should surveillance be undertaken? At what ages should it start and stop? What methods should be used?" Our collaborative studies with Norway, England and other European countries have shown that most breast cancers arising in young women at increased familial risk can be detected at screening from age 35 years onwards, using a combination of expert clinical examination an mammography (with ultrasound and biopsy as backup, where required). Twelve monthly screening intervals (but no longer for young women) are satisfactory and a starting age of 35 years or 5 years younger than the youngest affected relative means that few cases are missed. However, there is a case for looking further at a later starting age (perhaps 45 years) for some women with relatively weak family histories. Since risk, for many women, does not decline sharply at age 50 years, we should continue to collect data to establish whether continuation of screening, perhaps at 18 months intervals, is advisable up to age 55 years. For women who carry BRCA1 mutations, screening as currently practised, is unsuccessful although tumours may be detected at apparently early stages. The place of MRI for this group needs to be evaluated through longer follow-up.

Is surveillance cost-effective? For the great majority of women at increased familial risk, the answer appears to be "YES". My calculations suggest that the cost per QALY gained is of the order of £3,700. However, the possibility has not been excluded that some, at least, of the apparent "stage shift" from which these women benefit, actually stems from the favourable biology of familial cancer rather than as a direct result of the surveillance programme. For obvious ethical reasons, it is not possible to resolve that question at present.

What is the place of prophylactic surgery? For carriers of BRCA1 mutations, prophylactic salpingo-oophorectomy, with or without total mastectomy, is undoubtedly cost-effective. For carriers of BRCA 2 mutations, salpingo-oophorectomy, combined with lifetime mammographic surveillance appears to be a reasonable option. For all other women at increased familial risk of breast cancer, the only strong case for prophylactic surgery depends on disabling anxiety, for which alternative psychotherapy might be more appropriate. This presupposes that women will participate in a good quality surveillance programme—results of which are likely to be very satisfactory. Unilateral prophylactic mastectomy for carriers of BRCA1 or 2 mutations who have already been diagnosed with cancer in one breast raises difficult issues. With standard adjuvant chemotherapy the risk of contra-lateral cancer is low for several years, while the chances of relapse (distant metastases) from the initial tumour are high. Therefore a defensible position would be to delay a decision on further surgery for a year or two until it is clear that early spread of the initial tumour has not occurred. On the other hand, some women in this situation are very anxious to do everything possible to minimise their future risks and in several cases occult cancers have been found on pathological examination of the "prophylactically" removed breast. The message must be that each woman should be counselled and managed as an individual.

I hope to have contributed to the future of women at genetically increased risk for breast and ovarian cancer as well as demonstrating that the position of women at "low" genetic risk should be examined further, as there is now evidence to suggest that, for some at least, the risk may not be as low as initially believed.

Figure 8.1 summarises my views on how a regional breast cancer genetics service in Scotland should now be organised.

The specific changes from current practice are as follows:

1. GPs are encouraged to refer to the Regional Cancer Genetics service any women concerned about their family history of breats cancer.

2. Risk assessment is undertaken by trained professionals (genetics associates or genetics nurse specialists) with support from consultant clinical geneticists, using family history forms completed by the family and verifying, where necessary via clinical records, cancer registries and registers of births, marriages and deaths.

3. NICE criteria for eligibility for special surveillance programmes should be extended to Scotland and further adjustments to those criteria should be evaluated through longer follow-up of the Scottish "low risk" cohort described in Chapter 6.

4. Women known to carry BRCA1 or BRCA2 mutations or to have a family history placing them at increased risk of ovarian cancer should be offered prophylactic oophorectomy from age 40. This age criterion should be kept under review as some centres suggest oophorectomy at around 35 years of age.

5. Carriers of BRCA1 mutations (or those with a family history strongly suggestive of this) should be enrolled in regular MRI screening and the outcome of MRI-detected breast cancers should be monitored very closely. These women should also have the option of having bilateral prophylactic mastectomy performed.

6. Surveillance for women at moderate familial risk and who have a close relative or relatives affected over the age of 50 years should involve continued screening, at 18 monthly intervals, at least to age 55, before being discharged to the National Breast Screening Programme.

7. An important aspect must be provision for the gathering of further data to generate a secure evidence base for future modifications in the interest both of the NHS and of patients who rely on such a service.

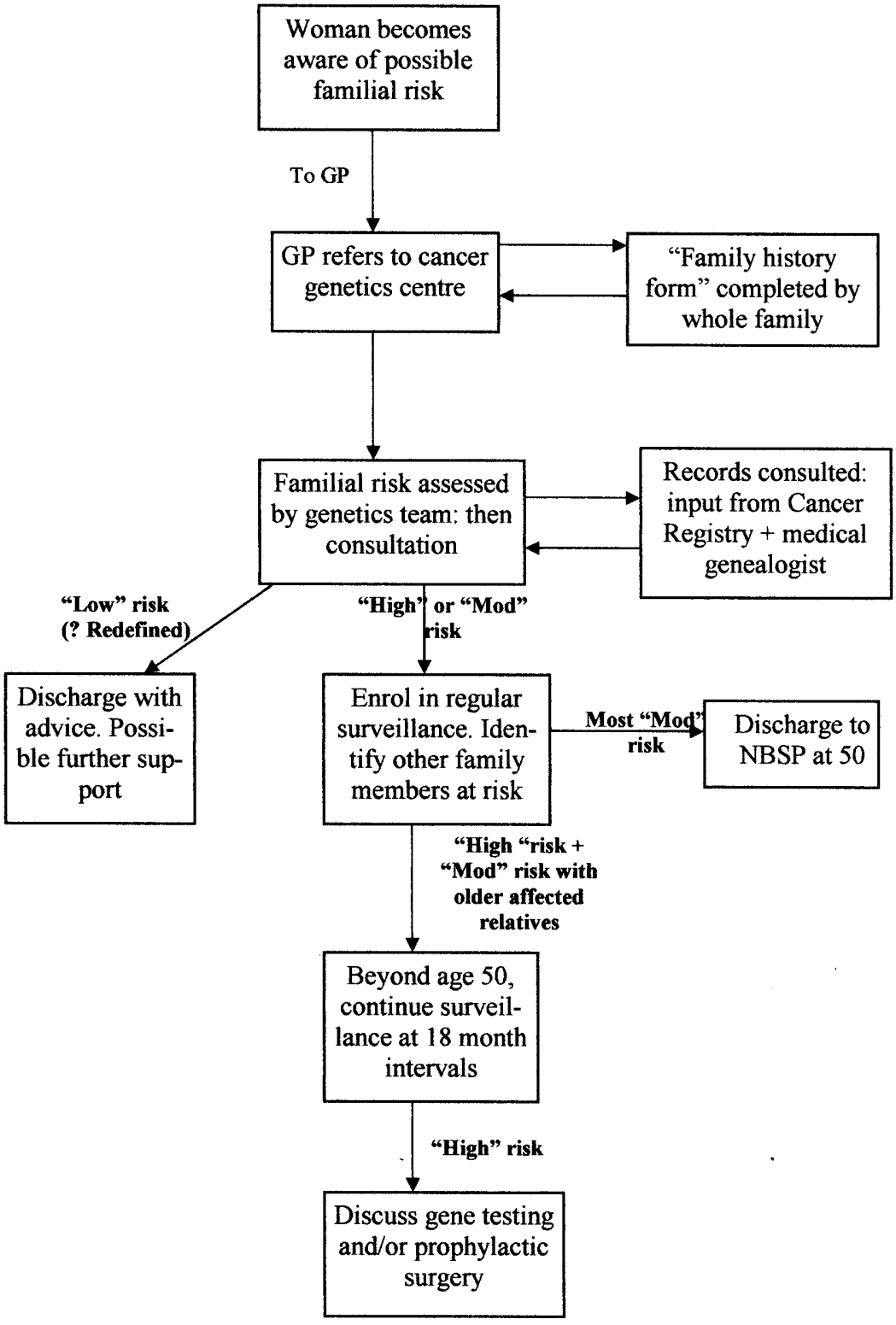

Figure 8.1: Optimal organisation of a regional breast cancer genetics service

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Appendices

Appendix A

Published papers

Disease Markers 15 (1999) 179–186
IOS Press

Efficacy of Early Diagnosis and Treatment in Women with a Family History of Breast Cancer

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ABSTRACT: BACKGROUND: Surveillance programmes for women at increased genetic risk of breast cancer are being established worldwide but little is known of their efficacy in early detection of cancers and hence reduction in mortality.
METHODS: Data were contributed from seven centres participating in the EU Demonstration Programme on Clinical Services for Familial Breast Cancer. All breast tumours (n = 161) detected prospectively, from the time of enrolment of women in a screening programme, were recorded. Analysis took account of age at diagnosis, whether tumours were screen-detected or not, their pathological stage and outcome by Kaplan—Meier survival plots.
RESULTS: Mean age at diagnosis was 48.6 years. Overall, 75% of tumours were detected in the course of planned examinations. For women under age 50 at diagnosis, this figure was 68%. Eighteen percent were mammographically negative, (23% in patients under age 50). At first ("prevalence") round and at follow-up screening, 16% and 22% of tumours respectively were carcinoma in situ (CIS) while 27% and 22% respectively had evidence of nodal or distant spread (CaN+). Comparison of screen-detected and other tumours showed that the latter were more frequently mammogram-negative and CaN+. Overall five-year survival was 89% and five-year event-free survival 86%. Five-year event-free survival was 100% for CIS, 88% for invasive cancer without nodal or distant spread and 67% for CaN+.
CONCLUSIONS: The majority of cancers arising in women at increased genetic risk of breast cancer can be detected by planned screening, even in those under

age 50. Surveillance should include regular expert clinical examination and teaching of "breast awareness" as well as mammography. Attention to the logistics of screening programmes may improve still further the proportion of tumours that are screen-detected. The trend towards earlier pathological stage in tumours detected during follow-up rounds and the preliminary findings on survival analysis suggest that this approach will prove to be of long-term benefit for breast cancer families.

KEYWORDS: Inherited, familial, breast cancer, prognosis, stage, diagnosis, survival, screening, mammography

INTRODUCTION

Familial breast cancer has been recognised at least since 1866 as a dominantly inherited trait characterised by early onset of disease and high mortality [1]. In many centres, systematic risk assessment and screening are now offered to female members of breast cancer families but there is little evidence from which to judge the effectiveness of these programmes. The few published reports have recorded small numbers of tumours prospectively diagnosed, documenting clinical and pathological stage but with no information on survival [2–5].

The demonstration that germline mutations in BRCA1 or BRCA2 underlie a substantial proportion of inherited breast cancers has made possible predictive testing to identify women at particularly high risk. This has stimulated debate on the relative merits of systematic screening versus prophylactic mastectomy as protective strategies [6].

The European Union has funded a multi-centre collaborative Demonstration Programme to evaluate clinical services for familial breast cancer. In all centres women are defined as eligible to receive these services if their genetic risk is at least twice that of the general population, based on the Claus model [7] (i.e. at least one first degree relative with breast cancer diagnosed before age 40 or one first degree and one second degree relative with breast cancer, mean age of diagnosis > 55years, or more than two close relatives affected — one first degree). We have described the surveillance programmes offered in the different centres [3,4,8]. Here we report the findings with respect to breast cancers diagnosed within these programmes, their means of detection, pathological stages and preliminary data on survival.

MATERIALS AND METHODS

Women were included in the present study if they were at sufficiently high genetic risk, as defined above, and, at enrolment, had no signs or symptoms suggestive of breast cancer (previous or concurrent). Numbers contributed from each centre are specified in Table 1. The period of study for each centre was from the time of establishment of a surveillance programme until the end of the latest month for which complete data are available. The date of enrolment for each woman was the date on which she was accepted for inclusion in a surveillance programme. In some centres, for logistic reasons, there could be a delay of several months between registration and first clinical/mammo-

Table 1
Numbers of tumours reported by centres

	Tumours
Norway	50
Dundee	29
Manchester	27
Leiden	20
Aberdeen	19
Edinburgh	14
Guy's Hospital, London	2
Sum	161

graphic examination.

Until very recently, entry to surveillance programmes in all the participating centres has been based on family history alone, since the availability of molecular diagnosis has been limited and DNA analysis has been applied mainly to families already enrolled in the programmes. The number of women with known BRCA1 or 2 mutations is still too small to be used as a grouping variable. They are therefore not treated separately in the analyses. All screening protocols include mammography (usually annually) from age 35 to 50 years, starting at a younger age if there has been very early onset disease in the family. This has been combined with regular expert clinical examination and instruction on self-examination of the breasts ("breast awareness"). For women over age 50, screening intervals in some centres have been longer (18 months or two years).

All centres have interpreted indications for cytology (fine needle aspiration and core biopsy) in this high-risk population liberally, placing the need for enhanced sensitivity ahead of concern for specificity. The frequency of invasive investigations has been evaluated for three of the participating centres. Rates were similar (3.9–7.3% of all examinations) and the extra demands on pathology services have been minimal [9].

Two of the participating centres have previously reported on prospectively detected cancers [3,4]. These series (updated) are included in the present report. Cancers were classified as carcinoma in situ (CIS), invasive carcinoma without evidence of spread (CaN_0) or invasive carcinoma with nodal or distant spread (CaN+), based on pathological findings after excision. Follow-up period was recorded as the time between definitive diagnosis and latest clinical examination. Tumours were designated "screen-detected" cancers if they were found on mammography, clinical examination, or both, within a planned surveillance programme. Those presenting outside a planned surveillance examination were either "interval" tumours (i.e. where there had been a previous negative screening examination) or "others" (to include those presenting clinically before a planned first screening examination was actually undertaken). The existence of this last group emphasises that evaluation of surveillance protocols for those at high risk must be based on "intention to screen" since delays in implementation of that intention, as well as unintended prolongation of screening intervals, may have adverse effects on programme performance.

Tumours were considered mammogram-negative if interpretation of the mammogram did not lead to additional investigations and/or if the radiologist could not confirm any suspicion of cancer raised by the clinical examination. Ten tumours (seven of which were non-screen-detected cancers) were excised without prior mammography. In calculating the proportion of mammogram-negative tumours, the denominator includes those not examined mammographically, unless otherwise stated. Contra-lateral breast cancer was treated as a separate tumour in recording stage at diagnosis, so nine patients were counted twice. However each patient was counted once only (using first tumour) for survival analysis, using Kaplan—Meier plots in the SPSS statistical PC programme. For overall survival, death was the event scored. For event-free survival, tumour spread (loco-regional, nodal or distant) or cancer-related death were recorded as events. For patients with metastatic disease at diagnosis, only death was scored as an event. No breast cancer patient in this series experienced any event (spread or death) which was not related to the first breast cancer recorded.

Age-specific mean sojourn time (MST or "lead time"), i.e. the time that a breast cancer may be detectable on examination before presenting clinically, was derived as follows. The average MST for breast cancer in this age group, (1.25 years) from published Swedish population studies [10,11], was applied to estimate the observation period covered by the first examination (the "prevalence round") and hence to deduce the annual incidence rate for our total high-risk population. The validity of this calculated rate was then tested by comparing it with the observed incidence rate on follow-up.

Predicted numbers of cancers were derived from local age-specific incidence rates. Statistical

associations were tested by Fisher's exact p (one sided).

RESULTS

One hundred and sixty-one breast cancers in 152 women were observed prospectively in women enrolled in formal surveillance programmes because of perceived genetic risk. This is by far the largest series reported from any such study. Mean age at diagnosis was 48.6 years, range 28 to 71 years, with 91 (57%) being under age 50, including 31 (19%) under age 40.

Table 2 records the characteristics of all the tumours observed, categorised by pathological stage, mammographic findings and whether they were screen-detected or not. Table 3 gives figures for women diagnosed before age 50 separately, but no statistically significant differences were seen between outcome in patients under and over 50 years of age.

We have previously published that annual incidence rate in the Norwegian series was 0.0064 calculated, as indicated above, from findings in the first round, and 0.0086 observed at follow-up [3]. Data from the Manchester series [4] allowed similar calculations, resulting in annual incidence rate 0.0025 derived from first round, and 0.0024 observed at follow-up. The closeness of agreement between calculated and observed data indicates that the assumed Mean Sojourn Time (MST) of 1.25 years is accurate.

Forty tumours (24.8%) presented clinically and were detected by the patients themselves. Two tumours were found on planned examinations outside the specific programme and, for the purposes of analysis, were classified as screen-detected. Among the 40 self-detected tumours, 2 (5%) were CIS, 22 (55%) were CaN_0 and 16 (40%) were CaN+. Compared with screen-detected tumours, interval and "other" cancers were less often CIS ($p = 0.01$) and more frequently CaN+ ($p = 0.006$). Thirteen out of 33 (39%) non-screen-detected cancers were mammographically negative (when examined on clinical presentation), versus 15 of 118 (13%) screen-detected ($p = 0.001$). Overall, 6 of 32 (19%) CIS, 16 of 87 (18%) CaN_0 and 6 of 32 (19%) CaN+ cancers were mammographically negative.

The proportion of CIS tumours was higher on

Table 2
Results stratified on CIS, CaN_0 and CaN+ for first round and for follow-up separately. Mammographic negative tumours (miming) and interval cancers (interval) in each row are specified. Percentages in parentheses were calculated as number in cell divided by sum for row

	CIS	CaN_0	CaN+	Sum	Mamneg	Not screen-detected
First round	8	29	14 (27%)	51	8 (16%)	11 (22%)[1]
Of these - mamneg	2	4	2 (38%)	8		5 (63%)[1]
- not screen-detected	0	6	5 (45%)	11	5 (45%)	
Follow-up	24	62	24 (22%)	110	20 (18%)	29 (26%)
Of these - mamneg	4	12	4 (20%)	20		8 (40%)
- interval	2	16	11 (38%)	29	8 (28%)	

[1] After filed "intention to screen" at genetic counselling, before first examination — time delay up to one year in some parts of the series.

Table 3
Results from follow-up (after first round) for patients aged less than 50 years considered separately

	CIS	CaN_0	CaN+	Sum	Mamneg	Not screen-detected
Follow-up	15	32	15 (24%)	62	14 (23%)	20 (32%)
Of these - mamneg	1	9	4 (29%)	14		5 (36%)
- interval	1	11	8 (40%)	20	5 (25%)	

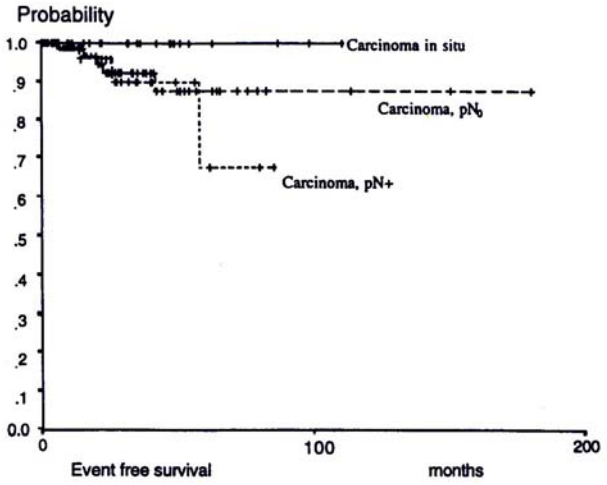

Fig 1. Event-free survival according to stage at diagnosis. CIS n = 32, CaN_0 n = 91, CaN+ n = 38.

follow-up than in the first screening round (22% vs. 16%); conversely, the proportion of CaN+ tumours was lower on follow-up (22% vs. 28%) but these differences did not reach statistical significance.

All deaths in the observation period were breast cancer related. Five year overall survival was 0.89 (SE 0.05). Five year event-free survival for the whole group of women with tumours was 0.86 (SE 0.06). Five year event-free survival for patients with CIS was 1; for those with CaN_0 it was 0.88 (SE 0.06) and for those with CaN+, 0.67 (SE 0.20) (Figure 1).

DISCUSSION

Women aware of their increased genetic risk of breast cancer have to make a difficult choice between enrolment in a surveillance programme, participation in a chemoprevention trial or prophylactic mastectomy. In the families described, few have actively pursued the last option but a recently published retrospective review [6], showing that surgery can reduce cancer incidence by 90%, has generated considerable interest and adds urgency to the question of how effective the alternatives may be, particularly in view of lack of empirical results for efficacy of mammographic and clinical follow-up examinations in premenopausal women at risk.

This study demonstrates conclusively that surveillance programmes for women whose family histories suggest they may be at increased risk can detect the majority of breast tumours, including those arising at an early age. Over 75% of tumours were detected in the course of planned screening examinations. Attention to the logistics of service provision might improve this figure still further: Eleven of the forty non-screen-detected cancers presented symptomatically in the period between registration of the patient for surveillance and institution of clinical/mammographic screening. In addition, seven of 11 (64%) interval cancers with spread at follow-up were detected more than 6 months after the previous examination (data not shown), indicating the possibility of reducing the numbers of pathologically advanced tumours by reducing the interval between screening examinations.

Sixty percent of non-screen-detected cancers were still node-negative at diagnosis. This may be interpreted as a success for the policy of

encouraging regular self-examination or "breast awareness". Nevertheless it is lower than the corresponding proportion of screen-detected tumours (82%) and is comparable to the figure for tumours in unscreened women under age 50 from the Swedish two counties trial [12]. Overall, twenty-eight tumours (18%) were negative on mammography despite the fact that the attention of the radiologist could be drawn to suspicious areas detected on clinical examination. This figure was higher (23%) for the tumours diagnosed under age fifty, though the difference is not statistically significant. These findings emphasise the need to include regular expert clinical examination as a component of screening for this high-risk group.

Rates of CIS were higher than expected in both the first and subsequent screening rounds (Table 2). The high frequency of CIS at follow-up was first noted in the Norwegian data [3] and is confirmed in the additional series reported here. If CIS was not associated with genetically-caused infiltrating cancers, the ratio of CIS to infiltrating cancers should have been relatively low in our cohort, enriched for women at increased genetic risk. The findings suggest that CIS is indeed associated with familial breast cancer and that, in the high-risk population, new CIS lesions are continuing to arise at an appreciable rate. In this setting, CIS is presumably a precursor of invasive cancer, in which case, one feature of an effective screening programme should be the trend observed here, namely an increasing proportion of tumours detected at the stage of CIS and a decrease in those with nodal or distant spread. This concept has parallels with inherited colon cancer where invasive cancer arises within the dysplastic adenomatous polyp and removal of the polyp protects against cancer [13]. It is also in keeping with a previous report that abnormal proliferation of the breast epithelium segregates as a dominant trait in breast cancer kindreds [14].

In this series, stage-specific 5-year survival was similar to that reported for sporadic breast cancer [15], while the overall 5-year survival was better. This again indicates that prognosis is related to stage at diagnosis, and that the effect of our intervention was mediated through diagnosis at an early stage.

The actual tumour incidence rates were much higher than age-specific rates for the general population but differed considerably between two centres (eight times higher in Norway, two and a half times higher in Manchester), which probably reflects differences in the risk profiles of the two clinic populations, given that a substantial proportion of Norwegian breast cancer families have subsequently been shown to carry founder mutations in BRCA1 [16], while there have been no comparable findings in Manchester. The only inference drawn from this part of the study was that familial breast cancer has the same age-related MST as sporadic cancer. Applying 1.25 year lead time [10,11] and comparing the outcome in this series with historical reports for BRCA1 mutation carriers [17,18], follow-up results to date are encouraging although several more years of observation will be required before the benefits of planned surveillance in this genetically high-risk group can be fully evaluated.

Inherited breast cancer is clearly not homogenous with respect to phenotypic appearance and prognosis. For example, there is evidence that tumours arising on a background of BRCA1 mutations are characterised by histopathological signs associated with poor prognosis, including low frequency of CIS [19]. If so, BRCA1 mutation carriers may need more frequent follow-up examinations because of a shorter "time-window" for diagnosis before spread. Our continued monitoring of the patients described, and determination of their carrier status for relevant mutations, may clarify this. The same problems of possible different effects of intervention for distinct genetic subgroups, also apply to any alternative strategy to prevent or cure inherited breast cancer.

While there remains a great need to match management strategies to more precise definitions of risk, women with family histories of breast cancer can now choose, on the basis of real data, between prophylactic surgery [6] and regular surveillance. It is interesting to compare these data with the predictions upon which a

published decision analysis [20] was based. The presumption that prophylactic mastectomy would confer 85% protection now appears slightly conservative, while the estimate that a screening programme would detect 80% of tumours at the node-negative stage (and 20% after metastatic spread) has yet to be confirmed, though these figures seem attainable. The conclusions that, "on average, 30 year old women who carry BRCA1 or BRCA2 mutations gain from 2.9 to 5.3 years of life expectancy from prophylactic mastectomy" and that "gains in life expectancy decline with age at the time of prophylactic surgery", are likely to prove accurate.

Acknowledgments

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SURVIVAL IN PROSPECTIVELY ASCERTAINED FAMILIAL BREAST CANCER: ANALYSIS OF A SERIES STRATIFIED BY TUMOUR CHARACTERISTICS, *BRCA* MUTATIONS AND OOPHORECTOMY

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Dedicated clinics have been established for the early diagnosis and treatment of women at risk for inherited breast cancer, but the effects of such interventions are currently unproven. This second report on prospectively diagnosed inherited breast cancer from the European collaborating centres supports the previous conclusions and adds information on genetic heterogeneity and the effect of oophorectomy. Of 249 patients, 20% had carcinoma *in situ* (CIS), 54% had infiltrating cancer without spread (CaN0) and 26% had cancer with spread (CaN+). Five-year survival was 100% for CIS, 94% for CaN0 and 72% for CaN+ ($p = 0.007$). Thirty-six patients had *BRCA1* mutations, and 8 had *BRCA2* mutations. Presence of *BRCA1* mutation was associated with infiltrating cancer, high grade and lack of oestrogen receptor ($p < 0.05$ for all 3 characteristics). For *BRCA1* mutation carriers, 5-year survival was 63% *vs.* 91% for noncarriers ($p = 0.04$). For CaN0 patients, mutation carriers had 75% 5-year disease-free survival *vs.* 96% for noncarriers ($p = 0.01$). Twenty-one of the mutation carriers had undergone prophylactic oophorectomy, prior to or within 6 months of diagnosis in 13 cases. All but 1 relapse occurred in the 15 who had kept their ovaries, ($p < 0.01$); no relapse occurred in those who had removed the ovaries within 6 months ($p = 0.04$) Contralateral cancer was more frequently observed in mutation noncarriers, but this finding did not reach statistical significance. Our findings support the concept that *BRCA1* cancer is biologically different from other inherited breast cancers. While current screening protocols appear satisfactory for the majority of women at risk of familial breast cancer, this may not be the case for *BRCA1* mutation carriers. The observed effect of oophorectomy was striking.

Key words: *breast cancer;* BRCA1; *oophorectomy; prognosis; survival*

Classified by aetiology, breast cancer is not a single disease. A minor fraction of cases are dominantly inherited. Inherited breast cancer is genetically heterogenous and attributable to mutations in several genes. The majority of cases in northern Europe are caused by genetic factors, so far not identified.[1,2] The prognosis of inherited breast cancer is a subject of debate.[3] Dedicated clinics have been established for the early diagnosis and treatment of high-risk groups,[4] but the effects of such interventions are currently unproven. One methodologic problem is that it is both ethically and practically impossible to randomise high-risk groups to assess the effects of interventions.

Eleven collaborating European clinical genetic centres joined forces through a Biomed2 demonstration programme on the management of inherited breast cancer. We published a preliminary report on the efficacy of early diagnosis and treatment, judged by stage at diagnosis and survival.[5] The activity continues as an open international research collaboration. The present report is a more comprehensive update on our series of prospectively identified breast cancers in high-risk groups, stratified by tumour characteristics, *BRCA1/2* mutation carrier status and the effect of prophylactic oophorectomy.

MATERIAL AND METHODS

Healthy women judged to be at risk for inherited breast cancer, according to preset criteria, were enrolled in follow-up programmes. For details of the inclusion criteria and follow-up programmes, see previous reports.[4,5] In brief, risk estimations were based on family history but without genetic testing prior to inclusion. Documented family history verified lifetime risk for breast cancer of 20% or more, implying that most women had a number of affected relatives. Genetic counselling was performed at the various clinical genetics centres. Follow-up surveillance included mammographic and clinical examination at least every year, in some centres every second year after the menopause. Informed consent and blood samples for diagnostic mutation analyses were obtained according to national legislation. All information was kept in medical files or approved research registers. All data were anonymous before export to the combined data set. The present report describes those patients in whom breast cancer was diagnosed for the first time at some point after enrolment in a surveillance programme.

We studied 249 patients from 4 European countries: Norway ($n = 87$), Scotland ($n = 79$), England ($n = 64$) and Holland ($n = 19$). Information on pTNM tumour stage, histopathologic grade (1, 2 or 3) and presence/absence of oestrogen receptors in infiltrating tumours was recorded. Our population included all patients contracting breast cancer within the observation period, irrespective of diagnostic methods. Most were demonstrated on planned examinations, but some were interval cancers (see previous report for detailed discussion[5]). Tumours were staged as carcinoma *in situ*

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(CIS, ductal or lobular), infiltrating cancer without nodal spread (CaN0) or cancer with spread (CaN+). All of the above data were collected from the medical files and not re-evaluated. For patients with bilateral cancer, *tumour characteristics* refers to the more advanced cancer for synchronous cases and to the first cancer for metachronous cases. More detailed subclassification is, of course, possible and will be appropriate when the data set has grown. Similarly, the material was stratified by country, rather than by participating centre, to ensure sufficient numbers in each group.

Blood samples for mutation analyses were obtained at diagnosis. *BRCA1* and *BRCA2* mutations were sought in all exons and splicing sites, using a number of methods and including specific search for all known local mutations, as previously described.[6,7]

Oophorectomy was recorded. Contralateral breast cancer, relapse and death were recorded as events. Any recurrence or cancer-related death was scored as relapse for CIS and CaN0. Death was scored as relapse for patients initially diagnosed with CaN+. Deaths not related to cancer were censored as unaffected. One non-breast cancer death was observed (oesophageal squamous cell carcinoma) and censored as unaffected. For calculation of contralateral cancer incidence, patients were censored at contralateral prophylactic mastectomy.

Associations were tested by χ^2 or Fisher's exact test. Differences between groups were estimated by *t*-test. Multiple regression was performed and survival estimated with the Kaplan-Meier algorithm using the Systat software package (SPSS, Inc., Chicago, IL). Point estimates for 5-year survival functions are given in the text; the corresponding Taron-Ware *p* values refer to total distributions.

RESULTS

Mean age at diagnosis for the 249 patients was 49.0 years (range 28–77, SD = 9.5). At diagnosis, 50/249 (20%) had CIS, 134/249 (54%) had CaN0 and 65/249 (26%) had CaN+ (including 1 with distant metastases). Mean follow-up time was 3.1 years (SD = 2.6, range 0–16). Fifteen patients had died, and 5 diagnosed with CaN0 had relapsed (Table I). Twenty-two patients had contracted bilateral breast cancer.

Thirty-six patients had truncating *BRCA1* mutations, and 8 had *BRCA2* mutations. Mutations were unevenly distributed according to country (Table II). The high prevalence of *BRCA1* mutation carriers in Norway reflects the local founder mutations.[7] There is no indication that cases attributable to founder mutations behave differently, in terms of the findings recorded in our study, compared to those having less frequent mutations. The number of *BRCA2* mutations was considered insufficient for statistical analyses, and the 8 *BRCA2* carriers were excluded from calculations on subgroups.

TABLE I – MUTATION STATUS VS. TUMOUR CHARACTERISTICS AND EVENTS

	BRCA1 mutation$^+$ (n = 36)	BRCA1/2 mutation$^-$ (n = 205)
CIS	1	48
CaN0	24	108
CaN+	11	49
Grade 1	1	22
Grade 2	7	62
Grade 3	18	43
Receptor-negative	19	31
Weakly positive	2	8
Receptor-positive	5	57
Events	8	12
Deaths	6	9

Mutation-carrying status *vs.* stage at diagnosis (χ^2 = 8.1, 2 df, p = 0.02). Mutation-carrying status *vs.* histopathologic grade in infiltrating tumours (χ^2 = 11.7, 2 df, p = 0.003). Mutation-carrying status *vs.* histopathologic grade in infiltrating tumours (χ^2 = 11.7, 2 df, p = 0.003). Mutation-carrying status *vs.* events (Fisher's exact p = 0.04). Mutation-carrying status *vs.* deaths (Fisher's exact p = 0.013).

Of the remaining 241 patients, 36 (15%) carried *BRCA1* truncating mutations; but only 1 of 49 (2%) CIS patients carried a mutation ($p < 0.01$). Details are given in Table I. *BRCA1* mutation carrier status was associated with high histopathologic grade and absence of oestrogen receptor in tumour tissue. For patients with infiltrating cancers, the mean age at diagnosis for *BRCA1* mutation carriers was 45.2 years compared to 50.3 years for noncarriers ($p < 0.01$).

Overall 5-year survival was 89% (Fig. 1). Five-year relapse-free survival was 87% (Fig. 2). Five-year survival without contralateral cancer was 90%. One (2.8%) of the *BRCA1* mutation carriers contracted bilateral cancer *vs.* 18 (8.8%) of the noncarriers (p = 0.18). There was no difference between cancers detected at first screen (prevalence round) and cancers detected at later follow-up.

There was no difference between countries for the above results, and all associations with mutation carrier status were as expected, except for the low incidence rate of bilateral cancer in *BRCA1* mutation carriers. Kaplan-Meier analyses on subgroups therefore treated the data as 1 series without further examination for heterogeneity.

Stratified by stage at diagnosis, 5-year survival was 100% for CIS, 94% for CaN0 and 72% for CaN+ (p = 0.007) (Fig. 3). Five-year disease-free survival was 100% for patients with CIS *vs.* 92% for CaN0 patients (p = 0.06).

For CaN0 and CaN+ patients grouped together, 5-year survival was 91% for mutation noncarriers and 63% for mutation carriers (p = 0.04) (Fig. 4). Among CaN0 patients, 5-year disease-free survival was 96% for mutation noncarriers and 75% for carriers (p = 0.01) (Fig. 5).

TABLE II – MUTATION-CARRYING STATUS ACCORDING TO COUNTRY (χ^2 = 26.4, 4 df, $p < 0.001$)

	BRCA1 mutation$^+$	*BRCA2* mutation$^+$	*BRCA1/2* mutation
Norway	24	0	63
UK	8	8	127
Holland	4	0	15

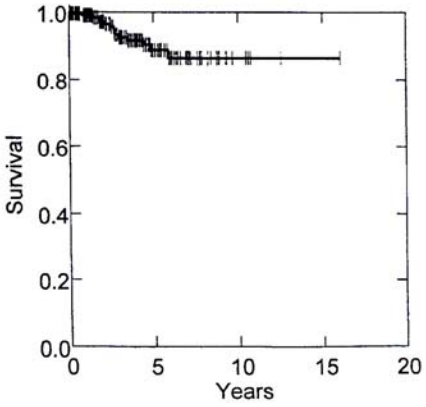

FIGURE 1 – Crude survival in whole series.

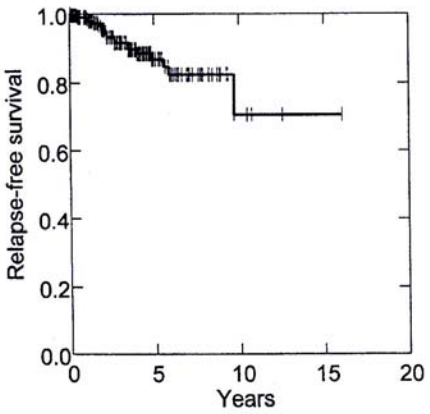

FIGURE 2 – Relapse-free survival in whole series (for definition of *relapse*, see text).

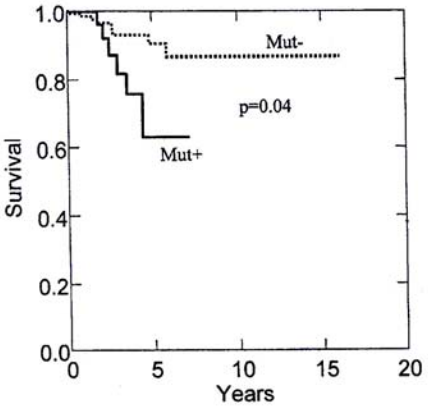

FIGURE 4 – Crude survival in patients with infiltrating cancers. *BRCA1* mutation carriers (Mut^+) *vs.* noncarriers (Mut^-).

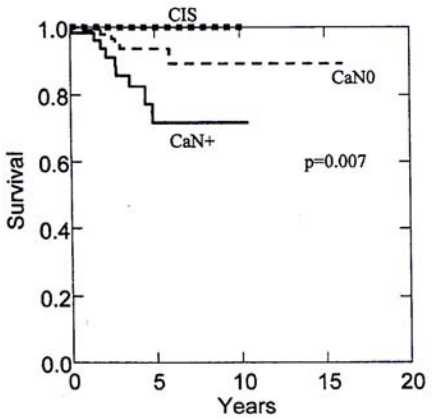

FIGURE 3 – Crude survival according to stage at diagnosis (for description of staging, see text).

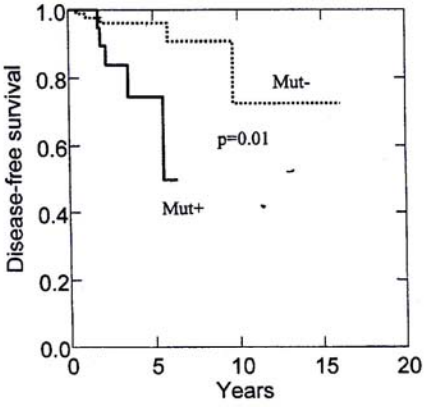

FIGURE 5 – Disease-free survival in CaN0 patients. *BRCA1* mutation carriers (Mut^+) *vs.* noncarriers (Mut^-).

For CaN0 patients, mutation status, grade and oestrogen receptor status were entered into a Cox regression model to assess associations with disease-free survival. Neither mutation status ($p = 0.10$), grade ($p = 0.62$) nor oestrogen receptor status ($p = 0.20$) was significantly associated with survival. Removing grade before repeating the calculations did not make either of the other 2 significant ($p = 0.10$ and $p = 0.18$, respectively).

In several of the collaborating centres, prophylactic oophorectomy, at around age 40, was advocated in breast–ovarian cancer kindreds, mainly to reduce ovarian cancer risk. Fifteen non-mutation carriers and 21 *BRCA1* mutation carriers had removed their ovaries. Among the mutation carriers, 4 had undergone prophylactic oophorectomy more than 1 year before breast cancer was diagnosed, 3 within 1 year prior to diagnosis, 6 within 6 months after diagnosis and 8 more than 6 months after diagnosis. All oophorectomies had been undertaken before relapse. Fifteen mutation-positive patients had retained their ovaries. One of 21 (4.8%) oophorectomized patients *vs.* 7/15 (47%) who had kept their ovaries experienced relapse ($p = 0.005$). Five-year survival for oophorectomized *BRCA1* mutation carriers was 67% *vs.* 44% for nonoophorectomized patients ($p = 0.01$) (Fig. 6). Five-year disease-free survival for oophorectomized CaN0 *BRCA1* mutation

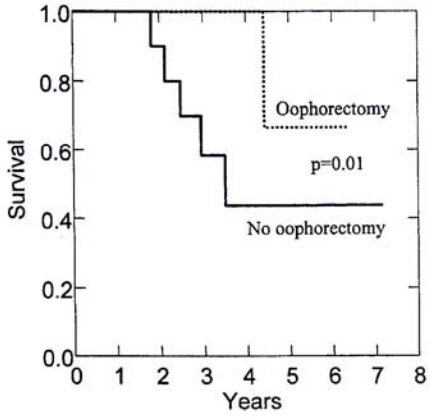

FIGURE 6 – Crude survival in *BRCA1* mutation carriers. Patients who had *vs.* patients who had not undergone oophorectomy.

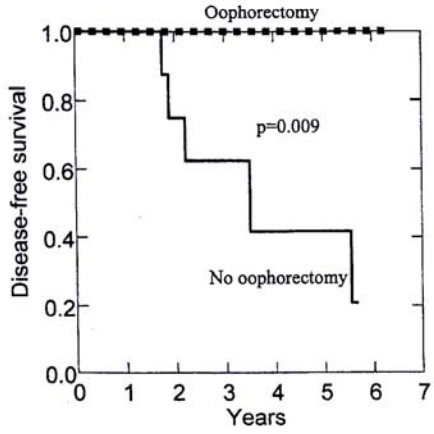

FIGURE 7 – Disease-free survival in *BRCA1* mutation CaN0 carriers. Patients who had *vs.* patients who had not undergone oophorectomy.

carriers was 100% *vs.* 42% for patients who had kept their ovaries ($p = 0.009$) (Fig. 7).

The first relapse in any *BRCA1* mutation carrier was recorded 1.8 years after the diagnosis of breast cancer. To eliminate the possibility that decision on oophorectomy might have been influenced by outcome of treatment, patients having undergone oophorectomy more than 6 months after diagnosis were excluded. Upon recalculation, the survival difference between the oophorectomized group and the others remained ($p = 0.04$), while the difference for relapse-free survival in CaN0 patients became marginal ($p = 0.06$).

DISCUSSION

Our results confirm that *BRCA1* mutation carriers present with biologically different cancers compared to noncarriers. Carriers have high-grade and oestrogen receptor-negative tumours, which are almost invariably infiltrating.[8] Both compared to the total remaining group and corrected for stage, survival was worse. All of these findings are in keeping with retrospective studies.[9,10] In addition, more than half of the *BRCA1* mutation carriers had had oophorectomy, and all but 1 relapse in mutation carriers occurred in women who had not undergone oophorectomy. A beneficial effect of oophorectomy in breast cancer is not a novel finding. It is also in keeping with previous reports on the preventive effect of oophorectomy in *BRCA1* mutation carriers[11] and on the preventive effect against contralateral cancer of tamoxifen in *BRCA1* mutation carriers.[12] In addition, we clearly demonstrate a survival advantage conferred by oophorectomy on *BRCA1* mutation carriers with breast cancer. Antioestrogens may prevent oestrogen receptor-positive breast cancer.[13] Oophorectomy is often discussed in relation to the effect of oestrogen, but no empirical data on protective effect of oophorectomy related to receptor status are known to the authors.

Because of the low numbers, all figures for survival may be regarded with caution, especially long-time survival. Long-time survivors are, however, an interesting observation; and they are presented, though no more than 38 cases (15%) were observed over more than 5 years. These cases confirm that the long-term survivors in the ascertainment clusters identifying families (data not shown) were not selection artefacts, at least not all of them. This information is important for genetic counselling. It is also of interest that long-term survivors with inherited breast cancer do not die of other cancers.

In conflict with retrospective reports,[14] we found a low annual incidence rate for contralateral breast cancer in *BRCA1* mutation carriers. Since the findings reflect not only the biology of the cancers but also the effects of treatment, we may speculate that the *BRCA1* cancers more often received adjuvant chemotherapy, which prevented second cancers. Although speculative, our findings may be interpreted as supporting the continuation of chemoprevention trials.[15,16]

No relapse and only 1 contralateral cancer occurred in the 15 patients without proven *BRCA1* mutations who had undergone oophorectomy, but the number in this group was insufficient for any statistical analysis. Similarly, because only 1 *BRCA1* mutation carrier developed contralateral breast cancer, the effect of oophorectomy on contralateral cancer among mutation carriers could not be addressed.

While it is possible that some *BRCA1* and *BRCA2* mutations remain to be detected in our patient group, the majority of inherited breast cancers were probably caused by a gene(s) so far not localized.[1,2] We previously reported that the number of prospectively demonstrated cancers in high-risk clinics greatly exceeds the predicted rate for an age-matched, unselected population.[17] The interpretation that non-*BRCA1/2* mutation carriers had breast cancer attributable to genetic factors was further supported by the high incidence of bilateral cancer. Our findings indicate that, in contrast to *BRCA1*-associated cancers, other forms of inherited breast cancer can be diagnosed as CIS and, in general, have a favourable prognosis.[8] Genetic testing for germline mutations may therefore be seen as a practical procedure to inform the choice of preventive strategies and treatment modalities. Although, in the present series, most of the germline mutations were detected after the diagnosis of breast cancer, advances in molecular technology mean that this is unlikely to be the normal situation in the future.

Oophorectomy has already been suggested as a management option in breast–ovarian kindreds and in *BRCA1/2* mutation carriers.[18] A major consideration was the risk of ovarian cancer in mutation carriers combined with the poor prognosis.[19] Oophorectomy may be considered a modality to prevent[11] and, now, to treat

breast cancer in *BRCA1* mutation carriers. As mentioned above, however, our findings should be confirmed in other series before firm conclusions are drawn.

Our study was initially undertaken to estimate the efficacy of surveillance in high-risk groups and compare it with the reported effect of prophylactic mastectomy.[20,21] The present findings extend and confirm the preliminary report from the same series.[5] The results indicate that groups of patients may benefit differently from the surveillance programmes and treatment given so far.

The present results highlight the need to take account of genetic heterogeneity and the putative beneficial effects of oophorectomy in *BRCA1* mutation carriers. As a substantial proportion (even the majority) of mutation carriers at some centres now choose oophorectomy, comparisons with historical data on patients treated differently (*e.g.*, prophylactic mastectomy in patients with unknown mutation status and without oophorectomy) may provide only limited information to guide decisions on therapy for future patients.

To evaluate the influence of mutation status on outcome, the usual procedure of selecting controls matched for age and tumour characteristics may be inappropriate because *BRCA1* tumours differ for most of the relevant characteristics (grade, stage, oestrogen receptor). When stratification is based on aetiology, breast cancer has a worse prognosis in *BRCA1* mutation carriers.[10] Matched for prognostic factors, differences between groups reportedly disappear.[22] Regression analysis of the CaN0 patients in our series did not support the notion[10] that mutation status has an impact on prognosis independent of grade and receptor status.

Among women enrolled in management programmes for familial breast cancer, the majority are well served by current screening protocols. However, a minority with *BRCA1* germline mutations fare significantly worse, even though detection of breast cancer at an apparently early stage (CaN0) is achieved for two-thirds of them. For *BRCA1* mutation carriers, therefore, it is essential to gather further data that will permit thorough evaluation of alternative management options, such as improved modalities for early diagnosis (magnetic resonance), chemoprevention or prophylactic surgery.

As mentioned above, all studies like ours face the methodologic problem that randomised trials are neither ethically nor practically possible. Some of the flaws of retrospective studies may have been overcome in our prospective series. However, discrepancies between our results and retrospective reports may also reflect time-related changes in treatment. Also, our selection model employing family history may not give results representative of inherited cancer selected differently. Our study is continuing and expanding. The results are recent observations without control groups, and for the present, conclusions should be interpreted with caution.

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Analysis of referrals to a multi-disciplinary breast cancer genetics clinic: practical and economic considerations

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Abstract Analysis of activity was undertaken in an established regional clinic providing risk assessment, counselling, screening and management for women with a family history of breast or ovarian cancer. The objectives were to determine: (1) how closely the route and pattern of referrals matched official guidelines (2) whether the previously recorded socio-economic imbalance among clinic clientele persisted and (3) the economic and practical consequences of committing resources to verification and extension of reported family histories. The findings were: (1) after some years of operation, the proportion of referrals direct from primary care had increased from less than 50% to over 75%, with a concomitant slight decrease in overall referral rate; (2) the socio-economic distribution of patients referred had become less selective and (3) extension and verification of reported family histories led to a redistributuion of risk categories, increasing the proportion of referrals judged to be in the ''low risk'' category, from 25% (based on referral letter alone) to 41% (at the end of the process). The costs associated with this approach are offset by the savings generated and it allows specialised counselling and screening services to be targeted more efficiently.

Keywords Breast cancer · Familial · Genetic · Clinical services · Risk · Assessment · Economics · Primary care

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Introduction

The past decade has seen rapid growth and evolution, in most developed countries, of clinical services for healthy individuals who may be at increased genetic risk of common cancers [1–3]. Such services aim to provide risk assessment, counselling, surveillance and/or intervention and, in appropriate circumstances, molecular genetic testing. To target limited resources effectively, it is necessary to set threshold levels of risk for referral to specialist genetics and/or surgical clinics. Specifications for these thresholds are now widely agreed and are reproduced in a number of authoritative guidelines that are applied in Europe, North America and Australia [2–5]. An example, for familial breast cancer, is given in Table 1. The expectation is that individuals at low risk will be ''screened out'' at primary care level. In the UK, efforts have been made to provide educational support packages for General Practitioners and other professionals in primary care, to enable them to fulfill this ''gatekeeper'' role with confidence [6] but there is substantial evidence that many feel uncomfortable, concerned at their lack of sufficient time

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Table 1 Risk classification and referral guidelines for familial breast cancer[a]

Risk status	Definition	Recommended management
''Low''	Anyone not fulfilling medium or high-risk criteria	Refer to National Breast Screening Programme at age 50
''Medium''	One first-degree relative with bilateral breast cancer (any age) or with unilateral breast cancer under age 40 or male first-degree relative with breast cancer (any age)	Physical breast exam annually from age 35 or from 5 years younger than youngest affected relative. Mammogram 2 yearly to age 40, then annually
	Two first- or first and second-degree relatives with breast cancer under 60[b] or ovarian cancer any age (same side of family)	
	Three first- or first and second-degree relatives with breast or ovarian cancer at any age (same side of family). At least one must be first-degree relative unless history via father	
''High''	Known carrier of mutated BRCA1/2 or other predisposing gene	Offer direct gene test
	First-degree relative of mutation-carrier	Physical examination annually from 35 or 5 years younger than youngest recorded cancer in family. Two yearly mammograms to age 40, then annual (18 monthly after age 50)
	First-degree relative of affected member of family with four or more cancers of breast or ovary (second-degree if history via father), or one first-degree relative (second-degree via intervening male). (Bilateral breast cancer counts as two.) Cases of ovarian cancer and of male breast cancer given added weight	

[a]Slightly modified from Ref. [4]

[b]NICE guidelines (2004), Ref. [5], remove age restriction

and expertise to discharge the responsibility [7–12]. Similar concerns have been reported from Switzerland [13].

A survey of 22 cancer family clinics operating in the UK [14] found that some 27% of all referrals did not appear to meet the minimum risk criteria for attendance at a specialist centre. For the four Scottish clinics included, the proportion was even higher (around 33%). However it is difficult to interpret these figures because there is no uniform standard for verification of reported family histories, and hence of risk status. Comparable analyses have not yet been reported from other countries but informal contacts confirm that UK experience is not atypical. The present study was undertaken, in part, to measure the effects of a sequential approach, applying increasingly rigorous checks on reported family histories of cancer. At the same time, an audit was undertaken of referral rates and routes of access to the breast cancer family clinic and of the socio-economic status of clinic clientele, since concerns have been expressed about the potential scale of demand [12, 15], about the disproportionate number of referrals coming, not from primary care but, indirectly, via specialist breast units and about over-representation of women from social class one, with under-representation of those from the most deprived section of the population [11, 16–19].

Methods

The setting was the Tayside multi-disciplinary breast cancer genetics clinic, staffed by personnel from the regional breast unit, the NHS radiology (breast screening) service and the regional clinical genetics service. It serves a population of some 500,000, operating within an NHS Scotland network of regional cancer family clinics covering the whole country. Although the Tayside clinic has been functioning since 1994, the specific study covers a period of 30 months from August 2000 to January 2003.

At the start of the study period, all General Practices in the Tayside catchment area (which includes North Fife) were issued with a breast cancer genetics ''information pack'' developed by the CRC Primary Care Education Research Group at Oxford [6], and modified, with the agreement of the authors, to refer specifically to Scotland. They were also reminded by letter and through presentations at GP study days and other locally-arranged seminars, about the functions of the breast cancer family clinic and informed of the proposed analyses. Continuing information was provided through the website of the Department of Surgical and Molecular Oncology, University of Dundee and through reports in the Tayren (Tayside Primary Care Research Network) newsletter.

Source and route for all referrals were noted. Employment status was also recorded and, together with post-code (which correlates with deprivation category), was used to create a socio-economic profile of women reached by the service.

All healthy women referred to the Tayside breast cancer family service were asked to complete (as far as they could) and return a detailed family history form, providing information on family structure and any cancers that had occurred among relatives. They were also invited to enter a

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trial, within which women whose genetic risk was judged to be below the guideline threshold level were randomised to receive the information, either by letter or by face-to-face interview, but without clinical or mammographic examination. Results of that trial are being reported separately. Its relevance to the present analysis is that it limited the numbers of women attending the multi-disciplinary breast cancer family clinic during the study period. On the basis of the family history form, a family tree was constructed by a genetics associate, who then instituted checking and extension of the data (with consent from living patients) via local and distant hospital records, Scottish Cancer Registry records and public records of births, marriages and deaths. The extent of this activity varied according to the apparent complexity of the family history but, for example, for 35% of referrals, use was made of the cancer registry-based professional medical genealogy service, provided by the Information and Statistics Division of NHS Scotland [20].

Women who did not complete or return their family history form, after one reminder letter, were generally offered an appointment at the multi-disciplinary clinic, where the history was recorded and staged verification or extension instituted, as above.

At the end of the staged process, cancer risk was determined by the genetics associate in consultation with a consultant clinical geneticist. When their judgement placed risk below the level at which regular surveillance would be offered [4], the woman referred was informed of the assessment and the reasons for it. A copy of the information was sent to her General Practitioner. No further contact with the cancer family clinic was arranged, but it was made clear that any relevant new information or developments (e.g. further instances of breast or ovarian cancer among relatives) should be notified to the cancer genetics service so that risk could be re-assessed. All such ''low risk'' women were reminded of the need to be ''breast aware'' and encouraged to join the UK National Breast Screening Programme (NBSP) from age 50.

Women whose assessed genetic risk was ''below threshold'', but who declined to take part in the randomised trial, were seen at the multi-disciplinary clinic, where they received breast examination by an experienced breast surgeon—many also had a mammogram—prior to discharge.

Results

Patterns of referral

There were 379 new referrals to the breast cancer family service within the study period (303 per year per million population). Over 75% of these referrals came directly from primary care, an increase of some 25% from the corresponding 1997 figure for the Tayside clinic and from the average reported in a UK-wide survey carried out in 1988 [14]. Furthermore, the social class distribution of Tayside service referrals evaluated in 1997 showed a substantial excess of highly educated, affluent women (38% with college diploma, university degree or higher professional qualification), including many with medical or nursing backgrounds, but a deficit of those from (the most deprived) social class 5. Virtually identical findings were recorded in Lothian, in France and in other centres, at around the same time [16–18]. However, a repeat audit of referrals to the Tayside clinic in 2001/2002, found that the proportion of highly educated women had fallen to 20% (comparable to the National average for women aged 40–50), while the social class distribution of breast cancer family clinic clients exactly matched that for newly diagnosed cases of breast cancer from the same catchment area [19].

For 24% of breast cancer family clinic referrals, no family history form was returned and a further 65 women (17% of total referrals, but 23% of those who did complete the form), declined to take part in the randomised trial. Two ''low risk'' women, who had agreed to take part in the trial, subsequently had their risk status altered and were enrolled in the multi-disciplinary clinic. Thus, overall, 87 of the 379 women referred (23%) were discharged as ''below threshold risk'', without clinical or mammographic examination, while 292 women were offered appointments at the multi-disciplinary clinic. Six of the latter moved to another area before their appointment date and 29 (9.9%) failed to attend, despite two reminder letters. Hence 257 women were seen at the multi-disciplinary clinic but 94 of these (37%) required no further follow-up, either because they had reached the age of 50 and could be discharged to the NBSP (26) or because they were judged to be in the ''low risk'' category (68). Thus, in total, 155 of the original 379 referrals (41%) were ultimately classified as ''low genetic risk'' and, according to guidelines, should have been ''screened out'' in the primary care setting. Under the system described, 68 of 257 women (26.5%) attending the multi-disciplinary clinic were at ''below threshold risk'' (Fig. 1).

Health care costs

As an example, the local cost implications of allowing ''low risk'' women to attend a clinic designed for surveillance and counselling of ''moderate'' or ''high risk'' patients are set out in Table 2, using official NHS figures for each element of cost. The total number of clinical examinations

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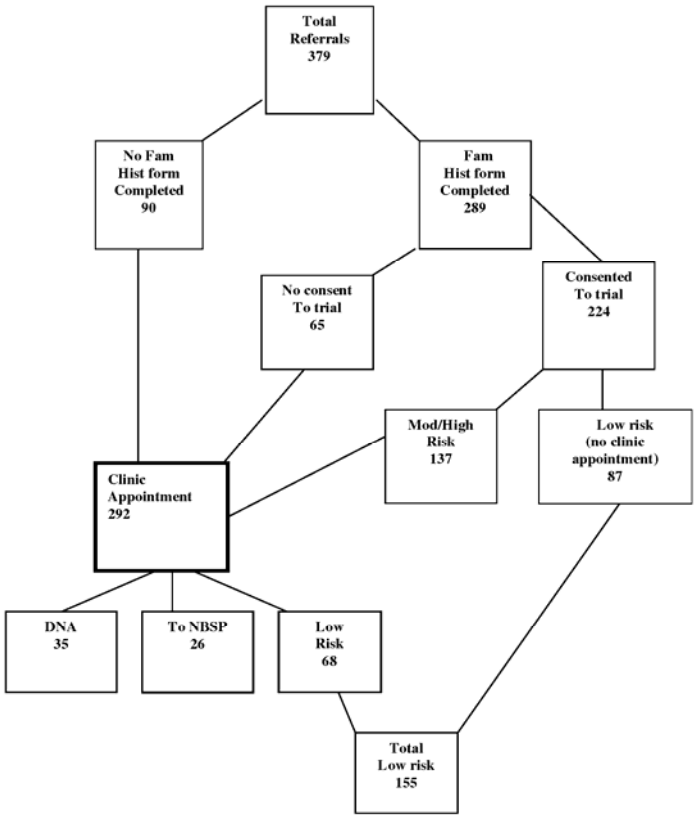

Fig. 1 Outcome of referrals to breast cancer genetics service

Table 2 Additional investigative procedures at familial breast cancer clinic

	Extra mammograms (£80)	Ultrasound (£65)	MRI (£400)	FNA (£100)	Core biopsy (£500)[a]
Total	20/172[b]	14/269	2/172	8/269	6/269
Low risk	6/42	7/77	0/42	6/77	6/77
Mod risk	12/106	7/157	2/106	2/157	3/157
High risk	2/24	0/35	0/24	0/35	0/35

[a]Costs per investigation derived from Tayside University Hospitals Trust ''blue book'' figures

[b]Number of additional investigations per mammogram (for extra views or MRI) or per clinical examination (for U/S, FNA or core biopsy)

(269) exceeds the number of patients seen because, in a few instances, women were recalled after a short interval, for example to check that a breast cyst had not recurred after aspiration. There is inexact correspondence between numbers of clinical examinations and mammograms, even for those at moderate or high risk, because several women had a mammogram within the preceding 12 months, while a few were seen for initial counselling before the age at which regular mammography is recommended. Nevertheless, for women at ''low'' risk, 77 clinical examinations generated 42 mammograms (of which 6 required extra views), 7 ultrasound examinations, 6 fine needle aspirations and 3

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core biopsy procedures, at a total cost of £8110 i.e. £119 per patient. None of these investigations in the ''low risk'' group led to the detection of a cancer.

Risk assessment

As described, risk assessment was undertaken in several stages, not all of which were judged necessary in every case. Table 3 sets out the changing distribution of referrals into ''low'', ''moderate'' or ''high'' risk (or ''unclassifiable''), categories after each stage of that process. There were multiple changes at each stage in all categories, with both upward and downward adjustment of individual risk estimates but the most striking feature is the increase in the proportion at ''low'' (i.e. ''below threshold'') risk as uncertainty is eliminated.

Discussion

Our findings indicate that, once cancer family clinics have been established for some years, the great majority of referrals come directly from primary care but, despite anxious predictions [12, 15], this is not accompanied by an unmanageable surge in referrals. In fact the rate of new referrals to the Tayside service, as elsewhere [21], appears to have reached a plateau that is somewhat below its peak of 4 years earlier. The more equitable socio-economic mix of clinic clientele is a welcome development that cannot be attributed to any specific action on the part of the regional genetics service. All of the above changes probably reflect growing familiarity with the local service among general practitioners and perhaps ''clearance'' of the backlog of ''multi-case cancer families'' known to their doctors before appropriate services became available.

There is, however, no indication that genetic risk assessment in the primary care setting (''gatekeeping'') is becoming more accurate. Our conclusion that some 41% of all referrals do not meet minimal criteria for attendance at the Tayside breast cancer family clinic supports comparable findings from Lothian, where similar checking protocols are followed [22]. The apparent deterioration compared with the 1997 national average figure of 27% cited earlier [14], is unlikely to be real but rather to reflect the inaccuracy of risk assessment without stringent verification of family histories.

Previous studies in many countries have indicated that word-of-mouth reports of breast or ovarian cancer among first-degree relatives are typically 80–95% accurate, which begs the question of whether further checks are justified. However, establishment of risk category often requires consideration of second and third-degree relatives. Age at diagnosis is frequently an important issue, as is the distinction between epithelial and other forms of ovarian cancer. In all of these respects, accuracy of initial accounts of family history may be much less than 80% [22–28] and, of course, when more than one instance of cancer in the family is taken into account, the overall error will be the sum of all the individual errors.

The fact that the Scottish population tends to show less mobility than in most parts of the UK, coupled with the unusually complete and accessible genealogical and Cancer Registry records [20] places Scottish clinics at an advantage when verifying and extending reported family histories. Nevertheless, the initial process of risk assessment, including use of self-completed family history forms, is much the same, with minor variations, in most cancer family clinics worldwide. Hence, our conclusion that intensive checking reveals many inaccuracies is likely to be valid for other countries also.

Where ''low risk'' women do reach a multi-disciplinary breast cancer family clinic, many of them receive a mammogram and some will have further investigations. These represent substantial costs, with little return, raising questions about why such investigations were undertaken in the present study. However, for many women (particularly those who had not returned a family history questionnaire), risk assignment could not be confirmed until after the clinic visit. Furthermore, when there is an expectation that the woman will be discharged, clinicians carrying out the examinations may be particularly concerned to ensure that no pathology is missed.

Table 3 Percentage of referrals placed in different risk categories at each stage of assessment process

Assigned risk	Information base for risk assessment		
	Referral letter (RL) only	RL+family history (F/H) form	RL+F/H form+full check[a]
Low	25%	30%	41%
Moderate	35%	57%	49%
High	6.5%	6.5%	10%
Unknown	33.5%	6.5%	0

These figures are based on a detailed analysis of 345 referrals

[a] ''Full check'', which includes scrutiny of relevant hospital records, Scottish Cancer Registry records and public records of births, marriages and deaths, was not required for all families but some elements were applied for over 50% of referrals

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Even without additional investigations, each visit to a breast cancer family screening clinic will cost around £100 (using UK National Health Service figures, as in Table 2) and, once admitted to a surveillance programme at age 35, a woman judged to be at ''moderate'' or ''high'' risk will be expected to attend for the next 15 years. Thus each incorrect inclusion of a ''low risk'' patient will incur a healthcare cost of at least £1500. For the Tayside clinic, with 150 new referrals per year, increasing the proportion categorised as ''low risk'' to 41% (from the national average of 27%)—i.e. eliminating 21 more patients from surveillance—saves over £30000 annually in current and future costs (appreciably more than the cost of the checking process). While costs and savings will vary in different settings, the above illustration will have some relevance for breast cancer family services in all countries. Equally—if not more—important is the observation that some referrals initially considered to be ''low risk'' are reassigned to a higher category in the course of verification.

Inevitably, there are some patients who are unable, or unwilling, to complete and return the family history questionnaire. The issue of how to deal with that situation remains unresolved. In Wales, for example, if there is no response after one reminder, the GP is simply told that the cancer genetics service will have no further contact with the woman. The GPs concerned have ''reluctantly'' accepted the need for this policy [12]. On Tayside, past practice was to offer clinic appointments to all women referred. Even during the study period, because the assessment process could not proceed in its absence, women who did not return a completed family history form were offered an appointment at the multi-disciplinary clinic, with the attendant costs documented here.

Discussions are now taking place with representatives of local primary care services to devise co-operative systems that will encourage better compliance with completion of family history questionnaires while making adequate provision for the minority who genuinely cannot comply.

Not even the most rigorous scrutiny of family history can guarantee that a given woman is truly at low risk of breast cancer and ''low'' does not mean ''zero''. On following our series of 379 women, we have recognised three occasions when the process we advocate led to underestimation of true risk. Furthermore, strict adherence to national guidelines still leaves room for error. For example, a patient seen by us at age 29, who had one close relative diagnosed at 39, was advised to return for regular surveillance from age 34 (5 years younger than the age of onset in her relative) but developed invasive breast cancer at 32. Nevertheless, we would claim that the sequential checking process we advocate reduces the overall error rate and achieves, to a substantial degree, the aim of concentrating specialist resources on those families most likely to benefit.

Our findings tend to justify the unease commonly expressed by GPs about their role as ''gatekeepers'' for cancer family clinics, since it is evident that accurate risk assessment requires more time and access to more records and expert support than are readily available in the primary care setting. Indeed the general recommendation [2–5], that specialist genetics input to clinical services for cancer families should be confined to those already identified as ''high risk'' would bear re-examination.

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Familial breast cancer: management of 'lower risk' referrals

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Up to 40% of referrals from primary care to 'breast cancer family clinics' prove to be of women whose assessed risk falls below the guidelines' threshold for management in secondary or tertiary care, despite recommendations that they should be screened out at primary care level. A randomised trial, involving 87 such women referred to the Tayside Familial Breast Cancer Service compared two ways of communicating risk information, letter or personal interview. Both were found to be acceptable to referred women and to their family doctors, although the former expressed a slight preference for interview. Only four women returned to their family doctors with continuing concerns about breast cancer. Nevertheless, understanding of information provided by either route was unsatisfactory, with apparent confusion about both absolute and relative risks of breast cancer. Substantial minorities appear to believe that they are at no increased risk at all, or even below the population level of risk, while others remain convinced that their personal risk has been underestimated. Family history record forms, completed by the referred women, preferably with the assistance of relatives, are crucial to full assessment of familial risk but one quarter of women referred to the Tayside Familial Breast Cancer Service currently do not complete and return these forms ahead of their clinic appointment. Further collaboration between primary care and the Breast Cancer Family Service is required to improve provision for concerned women whose risks fall below the threshold for special surveillance and to maximise effective use of the family history record form.
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Guidelines published in the UK recommend that women concerned about a family history of breast cancer should be assessed first in a primary care setting and only those whose risk exceeds a specified threshold should be referred to specialist services for counselling, screening and possible intervention (Harper, 1996; SIGN, 1998; Eccles *et al*, 2000; Haites *et al*, 2000; NICE, 2004). In reality, however, general practitioners (GPs) find this 'gatekeeper' role difficult, both in the UK (Fry *et al*, 1999; Bankhead *et al*, 2001; Rose *et al*, 2001; Walter *et al*, 2001; Elwyn *et al*, 2002; Campbell *et al*, 2003) and elsewhere (Escher and Sappino, 2000). The proportion of referrals to breast cancer family clinics that fall below the required risk threshold has been reported as almost 25% in one large UK-wide survey (Wonderling *et al*, 2001). For Scottish clinics that figure is 30–40% (Wonderling *et al*, 2001; Holloway *et al*, 2004; Reis *et al*, 2006), the difference probably being explained by greater ease of extension and verification of reported family histories in Scotland through access to the National Cancer Registry and to public records of Births, Marriages and Deaths (Collyer and DeMay, 1997; Brewster *et al*, 2004). The term 'low risk' is commonly used as shorthand, even in some official guidelines, to define those falling below the threshold, although such women are generally at greater risk (up to 1.7 times higher) than women of comparable age with no family history of breast cancer.

From its inception in 1994, the Tayside familial breast cancer clinic (TFBCC) has been a multidisciplinary service run and staffed jointly by the Departments of Genetics, Breast Surgery and Radiology. Before this study began, all women referred to the TBFCC were offered an appointment, even if the family history appeared to place them at 'low' risk. When that assessment was confirmed, no further follow-up would be arranged, although clinical examination (sometimes supplemented by mammography), was offered before discharge. Inappropriate inclusion of these 'lower risk' women in surveillance programmes probably does not represent cost-effective use of limited resources (Reis *et al*, 2006). However, the need to *'convey to individuals, especially those at low risk, accurate information in a sensitive and supportive manner'* must still be met (Harper, 1996). We report the outcome of a randomised trial of two approaches to this objective, together with difficulties encountered and possible solutions.

METHODS

Before the start of the study, which ran for 30 months from August 2000, all General Practices in the Tayside catchment area were issued with a breast cancer genetics 'information pack' developed by the Cancer Research Campaign (Watson *et al*, 2001) and

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modified, with the agreement of the authors, to refer specifically to Scotland. They were also informed by letter and through presentations at GP study days, and other locally arranged seminars, about the functions of the breast cancer family clinic and the planned trial. Continuing information was provided through the website of the Department of Surgical Oncology, University of Dundee, and through reports in the Newsletter of the Tayside Primary Care research Network.

With approval from the Tayside Research Ethics Committee, all women referred to the TBFCC were invited to participate in a trial, comparing provision of information about their familial risk by letter or by personal interview. This would apply only if they were judged to fall below the 1998 SIGN guidelines threshold for inclusion in a regular surveillance programme (SIGN and NICE thresholds are very similar). All referred women also received a standardised Family History Record form with a request to complete it as far as possible, preferably in consultation with relatives, and to return it as the first stage in their risk assessment. That form, together with the GP referral letter, augmented as appropriate in each case (and with relevant informed consent) by checking hospital records, Cancer Registry entries and Registrar General's Records of Births, Marriages and Deaths, provided the basis for a consensus decision, taken by the specialist genetics staff, whether to offer an appointment to the multi-disciplinary counselling/surveillance clinic. Enrolment in the trial thus required written informed consent, a completed Family History Record form and a clear decision that familial risk was below threshold level.

Women who met these criteria were randomised by a genetics associate (using computer-generated random numbers) to receive the information in a personalised letter or to attend the genetics department for an interview (with a genetics associate or nurse specialist) which gave an opportunity for questions to be asked and answered but did not include clinical breast examination or mammography. This was followed-up by a personal letter summarising the discussion. All letters included the information that, despite being below 'threshold' level, risk of breast cancer was still real. Women should therefore remain 'breast aware', report any breast symptoms promptly to their GP, notify TFBCC of any change in their family history of breast/ovarian cancer and participate in the National Breast Screening Programme from age 50. Letters were copied to the referring GP. The two subgroups were well matched for age and social class, the latter being assessed by postcode.

Three months after the letter or interview, participants in the trial were asked to complete and return a 'Satisfaction Questionnaire', based on the instrument used in the Wales 'TRACE' study (Brain *et al*, 2000; Gray *et al*, 2000). The constituent elements are listed in Table 1. They included standardised and validated measures of psychological health as well as specific reactions to the service received.

Eighteen months after the end of the trial period, all GPs who had referred patients included in the trial were asked to complete and return a short questionnaire to evaluate the service provided and specifically to gather information on whether the women had returned to their family doctors with continuing or fresh concerns about breast cancer.

For data analysis Statistical Package for Social Sciences (SPSS™) software was used.

RESULTS

During the study period, 380 women were referred to the TBFCC. Three quarters of these referrals came directly from Primary Care, the remainder being referred from the symptomatic breast clinic. Two hundred and eighty-one (74%) returned their 'Family History Record' form but 99 (26%) failed to do so, even after a personal reminder letter. Around half of these brought the form with them when they attended the clinic. Of those who did return the form, 64 (23%) did not give written consent to enter the trial. Only 18 of the 64 actively declined. The remainder simply did not return the consent document or returned it unsigned. Again, many brought the signed form to the multidisciplinary clinic but, even if 'low' risk status was confirmed, they could not then be randomised. There were therefore 217 women eligible for the study and, after full assessment as described above, 90 of these (41.5%) were judged to be below the guideline threshold level of genetic risk. They were therefore randomised to 'letter' (43) or 'interview' (47). Three were subsequently withdrawn; one, assigned to the 'letter' group, was found to have a cancer on initial examination at the symptomatic breast clinic (she had been referred there because of vague breast symptoms but family history had been mentioned in the GP letter and onward referral to the cancer family clinic had already been arranged, although no 'low risk' letter was actually sent). The other two provided, at interview, new information shifting them to the 'moderate' risk category. Among the other 45 'low risk' women interviewed, five gave new information requiring additional checks on family history and three mentioned breast symptoms that led to investigation by a breast surgeon but all remained in the 'low' risk category and no significant breast pathology was found. These data are summarised in Figure 1.

Seventy-one of the 87 randomised study patients (81.6%) completed and returned the 3 month 'satisfaction' questionnaire.

Table 1 Components of patient 'satisfaction' questionnaire

Element 1	Concerns about breast cancer Six questions, based on the breast cancer worry scale (Lerman *et al* (1991)). Each has four possible responses (tick boxes) indicating degree of worry
Element 2	Actions since receiving risk assessment Twelve questions about possible adverse effects on behaviour. Each has four possible responses indicating degree of adverse effect
Element 3	Experiences since receiving risk assessment Ten questions about possible positive effects on behaviour. Each has four possible responses, indicating degree of positive effect
Element 4	Understanding of breast cancer risks Eleven questions, five about perception of own risk, two about perception of general population risk, 1 about motivation for seeking risk assessment, three about remaining concerns and sharing them with family members. Answers were mainly options to tick or circle but own and population risk perceptions were presented both as a list of possible odds ('Inevitable ', ' 1 chance in 2', '1 chance in 3' through to '1 chance in 100') and also on a linear percentage scale, from 0 ('definitely will NOT get it') through to 100% ('definitely WILL get it')
Element 5	Experiences of the interview or written communication(s) with the clinic Twelve questions about amount of information given, whether it was understandable, whether questions were answered, whether risk given differed from expected, whether the process had helped in coping with perceived risk and whether the timescale for the process had been acceptable. Responses were mainly in the form of tick boxes with four options but free text space was included for expression of opinions
Element 6	General Health Questionnaire Twenty-eight item format with four subsections (Goldberg and Williams (1988))

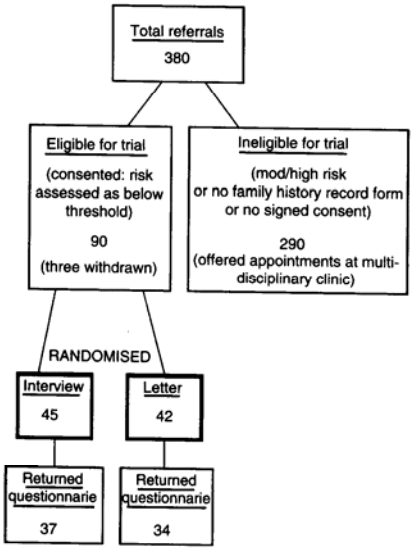

Figure 1 Distribution of referrals to the Tayside Familial Breast Cancer Service and recruitment to randomised trial.

The 87 patients had been referred by 82 GPs, of whom 64 (78%) responded to the follow-up questionnaire (with replies relating to 69 patients – 79%). Analyses of the responses are presented below.

Patient-completed satisfaction questionnaire

Independent samples *t*-tests were applied to all comparisons.

'Concerns about breast cancer' (6 items). Interitem correlations were good so the six were averaged to generate an index of breast cancer concerns. No difference was found between 'letter' and 'face-to-face' groups, $t(69) = -0.636$, $P = 0.527$.

'Actions since referral' (10 items). Correlations among items varied but all were significant. No differences between 'letter' and 'face-to-face' groups were significant.

'Experiences since referral' (12 items). Correlations between items were all significant so scores were averaged. The difference between averaged scores for 'letter' *vs* 'face-to-face' groups did not reach significance, $t(69) = -1.676$, $P = 0.098$.

'Personal breast cancer risk estimate'. There was a significant difference between 'letter' group (mean = 2.0) and 'face-to-face' group (mean = 2.38), meaning that those receiving their information at interview perceived their risk to be slightly higher than those informed by letter, $t(69) = -2.246$, $P = 0.028$.

'Concern about personal breast cancer risk'. No significant difference was found between 'letter' and 'face-to-face' groups, $t(69) = -0.705$, $P = 0.483$.

'Population lifetime risk of breast cancer'. Respondents were invited to estimate population risk in two formats (see Table 1). For one of these, five responses were missing. There was no difference between 'letter' and 'face-to face' groups for either item, $t(64) = .424$, $P = 0.673$ and $t(69) = 0.194$, $P = 0.846$.

'Your own lifetime risk of breast cancer'. Again, this question was posed in two formats. Five responses were missing for one of these. No significant differences between the trial groups were found for either format: $t(64) = 1.036$, $P = 0.304$ and $t(69) = -0.249$, $P = 0.804$. Both population and personal risk estimates were, however, often wildly inaccurate and there were poor correlations between estimates expressed in the two different formats by the same respondent.

'Satisfaction with the process'. For five of the 12 items in this set of questions, the 'face-to-face' group expressed significantly higher levels of satisfaction than the 'letter' group (P range 0.020–0.001) although the mean scores for the 'letter' group were in the 'quite satisfied' to 'very satisfied' range.

'General Health Questionnaire'. Scores for each of the four subgroups were summed and a *t*-test carried out on each. None of the differences between 'letter' and 'face-to-face' groups were significant.

In addition to the above quantifiable responses, women were invited to provide free text answers to open ended questions about their reactions to the information given. The majority either left these text boxes blank or indicated that they were content with the process. However, 7 (4 from the 'letter' and three from the 'interview' group) made statements indicating that they now believed they were at very low risk of breast cancer – possibly less than that of the general population. (*'I was happy to learn that it doesn't run in families and I am more relaxed about everything'. 'Quite happy that I am at considerably low risk'. 'Happy to know my risks are not increased by my mother having developed breast cancer'.*) A further seven (four 'letter', three 'interview') took the opposite view and clearly did not accept the judgement that they were at the lower end of the genetic risk spectrum (*'I cannot feel reassured by the response I received'. 'I don't know if I believe what you told me; you are giving me a result from statistics which can prove whatever you want to prove. You are not giving me medical facts'.*)

GP questionnaires

All but two of the 64 GPs declared themselves completely satisfied with the management of their individual patients. One had some reservations because of the time that elapsed (several months) between his referral and communication of the low assessed risk. Another was dissatisfied because he had no record of the outcome of his referral (although a copy letter had been sent to him).

When asked how they felt about a policy of evaluating risk before offering any clinic appointment and of declining appointments by explanatory letter for those judged to be below 'threshold' risk level, 46 of 64 respondents (72%) had no reservations. Seventeen had some reservations and one had serious reservations; where specific reasons were given, these related to the anticipated difficulty for some patients in completing a standard Family History Record form.

No patient had complained to the GP about the way in which their risk status had been assessed or communicated and only four had returned to the GP with concerns about breast cancer in the 18–48 months since receiving their clinic report. Two had fresh complaints of breast discomfort, which were investigated in the regional breast unit and two had simply wished to discuss the information from the genetics clinic. No breast cancers were recorded at that point but one other patient has subsequently developed invasive breast cancer at age 62 years.

DISCUSSION

Our findings show that in deriving the best possible estimate of future cancer risk, face-to-face interview adds little to a detailed family history form (particularly if completed as a collaborative project by several relatives) verified and extended by access to hospital, Cancer Registry and Registrar General's records. Communication of risk information and its implications, however, still presents difficulties.

Patients, whether informed by letter or by interview, seemed to be very uncertain of their actual risk level some 3 months later, at least when invited to give it a numerical value. The discrepancies between two alternative ways of presenting that information may suggest a lack of clarity in the questions or difficulties with numerical notation. Communication of risk in the setting of a breast cancer family clinic is well recognised as a problem area, with no method of communication proven to achieve accurate understanding (Watson *et al*, 1998; Cull *et al*, 1999; Braithwaite *et al*, 2004; Lobb *et al*, 2005). Furthermore, the free text comments from a number of respondents showed that, despite scrupulous avoidance of the term 'low risk' in oral and written communications from the clinic, some feel inappropriately reassured, to the extent of believing their risk may be below that of the general population. Conversely, others evidently cannot accept that their risk does not justify special screening (ineligibility for mammography being resented). Overall, the mean level of satisfaction with the process was acceptable, lying between 'quite satisfied' and 'very satisfied', although the scores for the 'interview' group were significantly better than for those receiving the information by letter. There were no significant differences between 'letter' and 'interview' in subsequent measures of cancer worry, nor of general psychological health. Despite the recorded preference for face-to-face communication, only four women had returned to their GP with concerns about breast cancer and two of these had been in the 'interview' group.

The GP questionnaires revealed no preference for either method of delivering the risk evaluation and, in general, a process whereby referred patients were assessed without necessarily being seen in person at a genetics clinic was considered acceptable.

CONCLUSION

Given that there must be a threshold level of risk below which clinical and mammographic screening cannot be offered, some disappointment, and hence dissatisfaction with the service is inevitable. Studies, including one from Scotland (Julian-Reynier *et al*, 1996; Lalloo *et al*, 1998; McLeish, 2003), have shown that women with a family history of breast cancer place access to regular mammography as their highest priority and indeed, so long as that is provided, they are content to forego specialist genetic assessment and counselling (Brain *et al*, 2000). The counterpart of that is that some women, when told their risk falls below guidelines' threshold, will resent exclusion from a surveillance programme. Several women used the free text boxes to express disappointment that they had not received any screening or 'professional examination' or to comment that they were relieved to know they would receive regular mammography from age 40 years (through a workplace or private healthcare scheme). Our findings in this regard are consistent with those of Scott *et al.* (2005) who interviewed a selected group of eight women judged to be at below threshold risk level and noted that several of them wished to have their risk 'up-rated' so that they would become eligible for screening.

No procedure, short of providing universal access to regular mammography, is likely to satisfy all women and any method of risk assessment will prove flawed in individual cases, as we have found. Nevertheless, our findings suggest that for most women at the lower end of the familial risk spectrum, communication of this information does not require a personal interview. A letter can be an adequate substitute. There is still scope for improvement without incurring unjustifiable costs. For example, the letter might include an invitation to contact the Genetics Centre to discuss continuing concerns. There may be a place for group sessions with specialists such as dieticians, counsellors and breast care nurses, where information on risk reducing 'lifestyle' modification may be offered and questions can be answered. Particular attention must also be given to methods of explaining risk, perhaps making use of high quality, specifically designed leaflets. Generic literature available from patient support groups, cancer charities and other clinics may also be useful but it will be important to harmonise the information they contain (Ozakinci *et al*, 2006).

The concern raised by several GPs about women who find it difficult to complete a Family History Record needs to be addressed. The fact that noncompletion of this form previously guaranteed access to the multidisciplinary clinic was perhaps a disincentive to its proper use and insistence on return of the form as a precondition for access to the cancer family service will almost certainly improve compliance. Rather than simply rejecting referrals in the absence of a completed form, however, it seems preferable to enlist the support of the primary care team in establishing why it has not been returned and in assisting those with genuine difficulties to collect and collate whatever family information may be available.

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Surveillance for familial breast cancer: Differences in outcome according to *BRCA* mutation status

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Women with a family history of breast cancer are commonly offered regular clinical or mammographic surveillance from age 30. Data on the efficacy of such programmes are limited. Clinical, pathological and outcome data were recorded on all breast and ovarian cancers diagnosed within familial breast cancer surveillance programmes at collaborating centers in Norway and the UK up to the end of 2005. These have been analyzed according to the mutation status of the affected women (*BRCA1*+ve, *BRCA2*+ve or mutation-negative). Breast cancer was diagnosed in 442 patients subsequently followed for a total of 2095 years. Eighty-nine (20%) had *BRCA1* mutations, 35 (8%) *BRCA2* mutations and in 318 (72%) no mutation could be detected ("mut neg"). Five-year survival in *BRCA1* was 73% compared to 96% in *BRCA2* and 92% in mut neg ($p = 0.000$). Among *BRCA1* mutation-carriers, 5-year survival was 67% for cases diagnosed as carcinoma *in situ*, 84% for node-negative invasive cancers and 58% for those with nodal involvement ($p > 0.05$). For *BRCA2* mutation-carriers the corresponding figures were 100, 100 and 90% ($p > 0.05$), while for mut neg women they were 100, 97 and 71% ($p = 0.03$). Regular surveillance in women at increased familial risk of breast cancer is associated with a good outcome if they carry *BRCA2* mutations or no detectable mutation. Carriers of *BRCA1* mutations fare significantly worse, even when their tumors are diagnosed at an apparently early stage. The differences in outcome associated with different genetic causes of disease were associated with demonstrated differences in tumor biology. The findings demonstrate the outcome for genetically different breast cancers detected within a programme for early diagnosis and treatment, which is relevant to genetic counseling when women at risk have to chose between the options for preventing death from inherited breast cancer.

Key words: *BRCA1*; *BRCA2*; breast cancer; inherited; outcome; prospective trail; early diagnosis

Inherited breast cancer may be caused by mutations in *BRCA1*, *BRCA2* or, rarely in other genes such as *p53* or *PTEN*.[1] In the majority of cases, however, no such mutations are found. Thus providers of services for familial breast cancer recognize three major groups: *BRCA1* mutation-carriers ("*BRCA1*"), *BRCA2* mutation carriers ("*BRCA2*") and women with no demonstrable mutation ("mut neg"). In terms of tumor characteristics, it is well established that *BRCA1* associated cancers differ from the others.[2–4]

Retrospective reports indicate that *BRCA1*-associated breast cancer has a bad prognosis[5–8] and we have confirmed, in a multi-centre prospective study of breast cancer in special surveillance programmes for those at increased familial risk, that *BRCA1* mutation-carriers have worse disease-free and overall survival than mut neg women.[9] Comparable data for *BRCA2* mutation-carriers have been limited. We have now doubled the follow-up period for the series already reported and have included almost 200 additional cases, making this by far the largest available dataset. In this report, we validate the previous findings on survival in "*BRCA1*" and "mut neg" women, adding new information on the relationship between pathological stage and outcome. We include the first report on survival of *BRCA2* mutation-carriers with breast cancer prospectively diagnosed within surveillance programmes.

Patients and methods

Healthy women at increased risk for inherited breast cancer, according to nationally set criteria, were enrolled in surveillance programmes. For details of inclusion criteria, surveillance protocols and follow-up programmes see previous reports.[9,10] In brief, risk estimation was based on family history but generally without molecular genetic testing prior to inclusion (mutation-testing was usually completed after diagnosis of cancer). Documented and verified family histories predicted lifetime breast cancer risks of 20% or more, indicating that most women had 2 or more affected close relatives. Genetic counseling was undertaken at the participating clinical centers. More recently, enrolment from families with identified mutations has increased as healthy relatives have been offered predictive testing, thereby increasing the prevalence of mutation-carriers within the total series. Surveillance included clinical and mammographic examination at least every year (in some centers at 18 month or 2 year intervals after the menopause). Informed consent and blood samples for diagnostic mutation analyzes were obtained in accordance with national and local ethical protocols. All cancer patients were managed according to standards applied at the diagnosing centre. All patient information was held in medical files or approved research registers. Data were anonymized before sharing for analysis.

All screen-detected and interval breast and ovarian cancers diagnosed up to December 2005, within the surveillance pro-

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TABLE I – NUMBERS INCLUDED, AGE AT DIAGNOSIS, FOLLOW-UP YEARS, ORIGIN OF PATIENTS, STAGE AT DIAGNOSIS, HISTOPATHOLOGICAL TUMOR GRADE, ESTROGEN RECEPTOR IN TUMOUR CELLS AND DEATHS STRATIFIED ON RESULTS OF *BRCA* MUTATION TESTING

	BRCA1		*BRCA2*		Mut neg		Sum	
	n	%	*n*	%	*n*	%		%
Total number in group	89		35		318		442	
Av age at diagnosis	43, 9		46, 2		50, 4			
Follow-up years	331		179		1,585		2,095	
Norway	61	69	8	23	123	39	192	43
UK	28	31	27	77	195	61	250	57
CIS	6	7	4	11	82	26	94	21
N0	56	63	20	57	172	54	247	56
N1	27	30	11	31	64	20	101	23
Grade 1	3	3	3	10	44	18	50	14
Grade 2	22	25	9	31	101	42	132	37
Grade 3	63	72	17	59	94	39	174	49
ER neg	54	72	6	26	47	21	107	33
ER ±	4	5	1	4	26	12	31	10
ER positive	17	23	16	70	150	67	183	57
Contralateral prophylactic mastectomy	6		3		14		23	
Prophylactic oophorectomy	38		7		22		67	
New primary breast cancer	2		8		20		30	
New primary ovarian caner	2		1		1		4	
New primary other cancer					5		5	
Death	16		1		21		38	

TABLE II – FIVE-YEAR SURVIVAL ACCORDING TO STAGE AT DIAGNOSIS AND RESULTS OF MUTATION TESTING

	All	CIS	N0	N+
BRCA1 mut + (%)	73	67	84	58
BRCA2 mut + (%)	96	100	100	90
No *BRCA* mut (%)	92	100	97	71
All	89	99	95	70

grammes, were identified. We record survival stratified by mutation status. This provides, for the first time, a substantial evidence base for the outcome of regular breast cancer surveillance, according to category of genetic risk.

Four hundred and forty-two patients are included. Information on pTNM tumor stage, histopathological grade and scoring of estrogen receptor (ER) status for invasive tumors was recorded. Between 70 and 80% of cancers were diagnosed in the course of screening examinations, the remainder being interval tumors.[10] There was no significant difference in sensitivity of screening between the 3 patient groups. Tumors were staged as carcinoma *in situ* (CIS), invasive cancer without nodal spread (CaN0) or cancer with nodal involvement (CaN+). All these data were collected from clinical files and were not subjected to re-evaluation. For the few patients with bilateral cancers, tumor characteristics refer to the more advanced one (for synchronous cancers) or to the earlier one (for metachronous tumors).

BRCA mutations were sought in all exons and splice sites using a range of molecular methods including, in some instances, MLPA assays for large deletions. Specific searches for recurring local mutations were undertaken as previously described.[11,12] One patient carrying both a *BRCA1* and a *BRCA2* mutation was included in the *BRCA1* group for analysis.

Breast and ovarian cancer deaths were censored as affected in survivor analyses on the assumption that the same underlying genetic cause accounted for either. One other cancer death was recorded (squamous cell carcinoma of oesophagus) and censored as unaffected. For calculation of contralateral breast cancer incidence, patients were censored at contralateral prophylactic mastectomy and, for calculation of ovarian cancer incidence, patients were censored at prophylactic salpingo-oophorectomy.

Associations derived from 2-by-2 tables are given as results of 2-sided Fisher's exact test. Differences between groups were estimated by *t*-test. Survival was measured using the Kaplan–Meier algorithm *via* Systat-10® software. Point estimates for 5-year survival functions are given in the text; the corresponding Taron-Ware *p*-values refer to the total distributions.

Results

Details are provided in Table I. Cancer was diagnosed in 442 patients who were followed for a total of 2095 years from diagnosis to latest review. Eighty-nine (20%) had *BRCA1* mutations, 35 (8%) *BRCA2* mutations and 318 (72%) were mut neg. *BRCA1* mutation carriers were younger than mut neg ($p < 0.05$) and had shorter mean follow-up, probably reflecting recent recruitment through predictive testing in kindreds with demonstrated mutations.

There was a difference in relative prevalence of *BRCA1* and *BRCA2* mutations between Norway and the UK, reflecting the different patterns of founder and other mutations in the 2 countries.[11,12] There were no differences in respect of stage at diagnosis, tumor characteristics or survival in the total UK series when compared with Norway so all cases were treated as a single series for further analyses.

Forty-five patients experienced relapse on 1 or more occasions, with 38 deaths. Thirty contralateral breast cancers, 4 ovarian (3 of these in mutation-carriers) and 5 other primary cancers were recorded. The latter comprised squamous carcinoma of oesophagus, malignant melanoma, basal cell carcinoma of skin, anal squamous carcinoma and chronic lymphatic leukemia.

Mut neg patients had a higher prevalence of CIS ($p = 0.0001$ *vs. BRCA1*; $p = 0.06$ *vs. BRCA2*). Mut neg had a lower prevalence of grade 3 tumors ($p < 0.0001$ *vs. BRCA1*; $p = 0.07$ *vs. BRCA2*). In contrast, *BRCA1*-associated tumors were more frequently ER-negative than either *BRCA2* or mut-neg cases ($p < 0.0001$ for both comparisons).

Table II records survival data. For the total series, 5-year survival was 89%, identical to the finding in our earlier report.[9] For the *BRCA1* group, overall 5-year survival was $\leq$84%, compared to $\geq$90% for the *BRCA2* group (any stage).

The *BRCA1* group had worse survival than *BRCA2* or mut neg (Fig. 1) ($p < 0.001$ for difference between all 3 groups; $p = 0.02$ for difference between *BRCA1* and *BRCA2* groups alone). In *BRCA1* cases, pathological stage at diagnosis showed no association with survival. One *BRCA1* carrier with DCIS had died from her breast cancer. Her DCIS had areas with microinvasion.

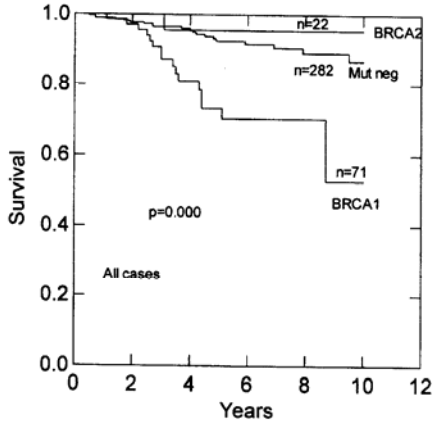

FIGURE 1 – Survival according to mutation demonstrated in the whole series.

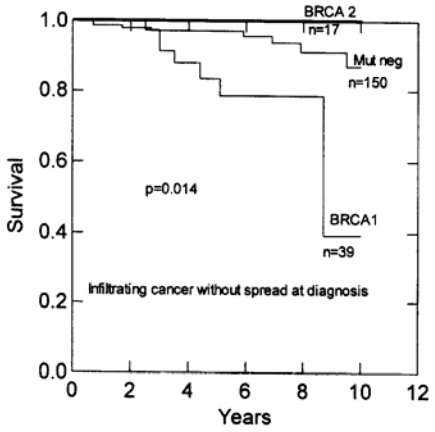

FIGURE 2 – Survival according to mutation demonstrated in infiltrating cancer cases without spread at the time of diagnosis.

Patients with node negative *BRCA1* tumors had a bad prognosis (Fig. 2; $p = 0.001$ for *BRCA1 vs.* other groups). In the *BRCA2* group only a single death was recorded so association with stage could not be tested. In the mut neg group, stage was correlated with survival ($p = 0.001$).

In parallel to our previous findings,[9] *BRCA1* mutation-carriers who had undergone oophorectomy had a trend of better survival than those who retained their ovaries, ($p = 0.07$, 5-year survival 79 and 66%, respectively). The same trend has been recorded by others.[7]

Twenty-three women underwent prophylactic contralateral mastectomy and 67 underwent oophorectomy. The *BRCA2* group had a higher prevalence of contralateral cancer ($p = 0.02$) accounted for by synchronous bilateral cancers. The annual incidence of other primary cancers was 0.0024, no higher than expected for women aged 50–54, according to data from the Norwegian and Scottish cancer registries.

Discussion

The findings confirm the good outcome of current surveillance and management protocols for mut neg women and that this applies equally to *BRCA2* mutation carriers. The differences in prognostic tumor markers between *BRCA1* and *BRCA2* carriers have long been known[13] and a difference in survival was not unexpected. There have, however, been conflicting reports, limited numbers included[14] and most reports have been retrospective.[8,15,16] This is the first prospective study to verify better survival in *BRCA2* mutation carriers compared to *BRCA1* within the follow-up systems employed.

In contrast, we confirmed our previous finding[9] that the outcome for *BRCA1* mutation carriers is unsatisfactory, even when tumors are detected, through screening, at an apparently early stage. These observations are consistent with other evidence that *BRCA1* tumors metastasis early and that nodal spread is not correlated with size of the primary tumor.[8,17] Five-year survival for the *BRCA1* group (any stage) was 74%, compared to 62% in our earlier report[9] and 73% in a recent retrospective study from the Netherlands.[7]

While considerable efforts have been made to identify all *BRCA1* and *BRCA2* mutation-carriers in this series, we recognize that a small proportion of those in our mut neg group may, in time, prove to be misclassified. The likely effect on our conclusions will be to increase the observed between-group differences in outcome.

Existing guidance on the management of inherited breast cancer risk is based largely on untested assumptions about the benefits of screening. In particular, the great differences in outcome for *BRCA1* and *BRCA2* mutation-carriers have not been recognized.[18–23] Increasingly, mutation status will be known before cancer develops. Hence the outcome of surveillance may be predicted and management policy adjusted accordingly.

The low incidence of new primary cancers and the paucity of ovarian cancers in our series (relative to the high incidence of first cancers in women with a strong family history) may indicate an effect of adjuvant chemotherapy even in *BRCA1* mutation carriers. Salpingo-oophorectomy is established as a worthwhile prophylactic procedure in *BRCA1* and *BRCA2* mutation-carriers[24,25] and our findings suggest that the procedure can also be of value as part of the management of breast cancer arising in these patients, but the numbers are limited and the findings are not conclusive. The question of its role for women still in their childbearing years remains unanswered.

Given the lack of correlation between primary tumor stage and metastatic spread for *BRCA1* tumors, the use of MRI as a screening modality may not result in the anticipated survival benefit[26] despite the growing evidence that it can detect these cancers considerably earlier than mammography.[27–30] Careful documentation of outcome for MRI-detected breast cancers will therefore be essential. New developments in chemotherapy may also improve the outlook for *BRCA1* mutation-carriers but, until that has been confirmed, the present findings should be taken into account when women with significant family histories of breast cancer make informed choices about their management.

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Prospective surveillance of women with a family history of breast cancer: auditing the risk threshold

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To evaluate current guidelines criteria for inclusion of women in special 'breast cancer family history' surveillance programmes, records were reviewed of women referred to Scottish breast cancer family clinics between January 1994 and December 2003 but discharged as at 'less than 'moderate' familial risk'. The Scottish Cancer Registry was then interrogated to determine subsequent age-specific incidence of breast cancer in this cohort and corresponding Scottish population figures. Among 2074 women, with an average follow-up of 4.0 years, 28 invasive breast cancers were recorded up to December 2003, where 14.4 were expected, a relative risk (RR) of 1.94. Eleven further breast cancers were recorded between January 2004 and February 2006 (ascertainment incomplete for this period). The overall RR for women in the study cohort exceeded the accepted 'cutoff' level (RR = 1.7) for provision of special counselling and surveillance. The highest RR was found for the age group 45–59 years and this group also generated the majority of breast cancers. The National Institute for Clinical Excellence ('NICE') guidelines appear to be more accurate than those of the Scottish Intercollegiate Guidelines Network ('SIGN') in defining 'moderate' familial risk, and longer follow-up of this cohort could generate an evidence base for further modification of familial breast cancer services.
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Keywords: breast cancer; familial; risk assessment

Genetics and Genomics

A family history of breast cancer is recognised as a risk factor for the disease. Most efforts to quantify that risk rely upon two retrospective studies (Claus *et al*, 1991; Collaborative Group on Hormonal Factors in Breast Cancer, 2001), both of which provide a range of estimates, based on the number of affected close relatives and their ages at diagnosis. These estimates, however, are derived from rather small numbers of women in some of the specific risk categories and have wide confidence intervals. The National Institute for Clinical Excellence (NICE) (2004) guideline on familial breast cancer concludes that 'validation of risk assessment models is urgently needed'. It is universally accepted that a woman under 50 years who has three or more close relatives affected with breast cancer (one at least being a first-degree relative or second degree if on her father's side of the family) is at sufficiently increased risk to justify special surveillance, with the object of detecting breast cancer early in women too young to be included in the National Breast Screening Programme (NBSP). If there are only two close relatives affected, SIGN guidelines stipulate that both must have been under 60 years at diagnosis, but NICE (both the 2004 version and the 2006 update) applies no such age restriction. Under either NICE or SIGN criteria, if there has been only a single first-degree relative affected, risk to sister or daughter is not considered to be significantly increased unless age at diagnosis was less than 40 years. Both guidelines also take account of ovarian cancer among relatives, attaching slightly greater weight to it than to breast cancer in assessing familial risk. A prospective evaluation of five different protocols for prediction of breast cancer risk from family history and other criteria (Amir *et al*, 2003) concluded that the most commonly applied models tended to underestimate risk, particularly for those at the lower end of the familial risk spectrum but, again, numbers were limited. We have therefore embarked on a prospective survey of cancer incidence among a large cohort of asymptomatic women discharged from breast cancer family clinics because their risk levels, based on reported family histories, were judged insufficient to warrant enrolment in special surveillance programmes.

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PATIENTS AND METHODS

Since 1994, clinical services for familial breast cancer have been provided for the whole of Scotland by a network comprising four

major centres in Aberdeen, Dundee, Edinburgh and Glasgow, involving close collaboration between medical genetics, diagnostic radiology and breast surgery units, with support from the Information Services Division (ISD) of the NHS Scotland Common Services Agency and the Scottish Cancer Registry. Two of the centres operate 'one-stop' clinics staffed by geneticists, breast surgeons and radiologists. The others provide comparable, but sequential, services in separate genetics and breast surgery clinics. In all four centres practice is based on guidelines formulated by the Scottish Office Home and Health Department (1998) and incorporated into Scottish Intercollegiate guidelines Network (SIGN) Guideline 29, 1998. These set a threshold, for the definition of 'moderate' familial risk, the major criteria being summarised above. Women referred to a breast cancer family service whose family histories meet or exceed these criteria are offered regular surveillance from age 35 (or 5 years younger than the earliest age of disease onset in a relative). Otherwise, they are discharged to primary care with reassurance, advice on being 'breast aware', encouragement to take advantage of the National Breast Screening Programme (NBSP) from age of 50 and a request to notify the cancer genetics service should any new breast or ovarian cancers occur within the family. The threshold requirements are in line with those proposed in the majority of published recommendations (Public Health Genetics Unit, 1998; Watson *et al*, 1999; Eccles *et al*, 2000; Haites *et al*, 2002; Breakthrough Breast Cancer, 2004; Nelson *et al*, 2005) but differ from NICE guidelines which remove any age-at-diagnosis restriction in the case of two affected relatives.

With local approval for audit purposes, the records of the four Scottish breast cancer family services were scrutinised to identify all referred women whose risk had been assessed, as below the 'moderate' threshold over the 10-year period from January 1994 to December 2003. Then, with consent from the Privacy Committee, Scottish Cancer Registry records were checked to detect any cancers recorded in this cohort of individuals. For breast and ovarian cancers, confirmation and further pathological details were sought from case notes.

For each woman referred to a cancer family clinic, but not offered continuing surveillance, the period elapsing between discharge from the service and December 2003 was calculated and, from that and the date of birth, the number of woman years of observation within one or more 5-year age spans (35–39, 40–44 and so on) was derived. The data were aggregated to give the total number of woman years of observation per 5-year age group and the corresponding 'expected' numbers of breast cancers were obtained from Scottish Cancer Registry figures, which report annual incidence for the same age groups. Where a breast or ovarian cancer had been recorded, the precise details of family history were re-checked in every case from cancer family clinic records. Cancers registered after December 2003 were noted and checked as above. Because registration is still incomplete for that period, these cases cannot be included in calculations of absolute or relative age-specific incidence but can be added to the earlier cases to record age distribution of cancers, their clinical and pathological characteristics and the proportions that would have met NICE criteria for inclusion in special surveillance programmes.

RESULTS

The principal findings are summarised in Table 1a and b and Figure 1. Within the main 10-year study period, 28 invasive breast cancers were recorded in 26 women out of the total cohort of 2074. The expected number was 14.4, giving an overall relative risk (RR) of 1.94 (95% CI = 1.3–2.8). As shown in Figure 1, the RR was not uniform for all age groups, the highest (>2.8) being for the 50–54 year olds. The 11 further breast cancers diagnosed since December 2003 are listed in Table 1b and included in Figure 2.

Two women had suffered synchronous bilateral breast cancers, in each case both tumours being detected at first NBSP mammogram at the age of 50 years. One had a family history that would have placed her in the 'NICE moderate' risk category (sister diagnosed at the age of 46 years, paternal grandmother in her 70's). The other had only one affected relative, her mother, diagnosed at the age of 70 years. She would therefore have been considered below threshold risk level for surveillance under any extant guidelines.

In addition to the breast cancers recorded in Table 1a and b, there were three instances of ductal carcinoma *in situ* (DCIS) and one patient in whom an unsuspected second focus of invasive ductal cancer was identified by the pathologist in the mastectomy specimen following surgery for a symptomatic cancer. Although this was considered a second primary, that could not be proved and it has not been treated as such in the present report. One additional case of DCIS was recorded in 2005 and has been excluded from calculations. More than half of all breast cancers

Table 1a Data on breast cancers among 2074 women discharged from the Scottish breast cancer family clinics, January 1994 to December 2003

Women-years of F/U:		Breast cancers expected (Population data)	Breast cancers recorded (Total cohort)	Breast cancers recorded (Excluding NICE 'moderate risk')
Age < 35	843	0.25	0	0
35–39	1341	0.8	1	1
40–44	1552	1.9	2	1
45–49	1522	2.7	4	3
50–54	1405	3.9	11	8
55–59	846	2.5	5	5
60–64	454	1.4	2	0
65+	320	0.95	3	1
Total	8283	14.4	28 (95% CI = 18.61–40.47)	19 (95% CI = 11.44–29.67)

	Node negative	Node positive
Invasive ductal carcinoma	13	6
Invasive lobular carcinoma	2	1
Invasive tubular carcinoma	4	0
Mixed types	2	0
Screen-detected = 18,	Symptomatic = 10	

were diagnosed at clinical or mammographic screening – mainly through the NBSP, but three at one of the multi-disciplinary breast cancer family clinics, where policy (until the year 2004) had been to see all women referred, even where their risk had been evaluated and the decision already taken to discharge them following that single visit. Since 2004, women whose risk has been assessed as below the 'moderate' threshold are no longer seen at the multi-disciplinary clinic and are not offered clinical examination or a mammogram before discharge.

Table 1b Breast cancers diagnosed in the study cohort since December, 2003

Age		
<35	0	
35–39	0	
40–44	1	(NICE 'moderate risk')
45–49	1	
50–54	2	
55–59	4	
60–64	3	(Two NICE 'moderate risk')
Total	11	7 screen-detected, 4 symptomatic: 10 invasive ductal, 1 papillary

Twelve of the 39 tumours (31%) occurred in women whose family histories would have placed them in the 'moderate' risk category had NICE, rather than SIGN guidelines been applied – that is, they had two affected close relatives (one first degree) at least one of whom had been over 60 at diagnosis. A re-examination of the family histories of our total cohort shows that only 10% would have been reclassified as 'moderate risk' under NICE criteria ('NICE moderate' subgroup).

There were three epithelial ovarian cancers (one each of serous, mucinous and endometrioid type) and one borderline ovarian

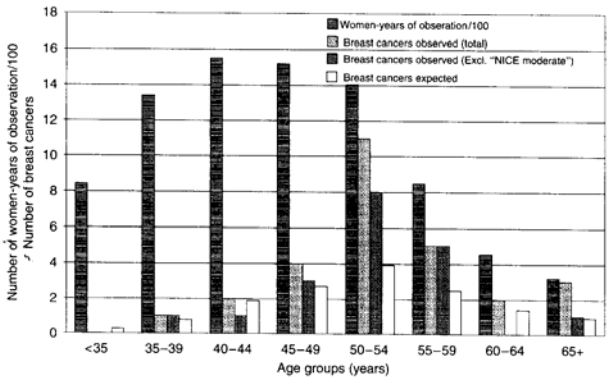

Figure 1 Age-group distribution of 28 invasive breast cancers recorded by the Scottish Cancer Registry from January 1994 to December 2003 among 2074 women discharged from the Scottish Breast Cancer Family clinics as being at less than 'threshold' level of risk: the same data but excluding cancers occurring among women whose risk would have been above the threshold under 2004 NICE guidelines ('NICE moderate' group) and expected distribution of breast cancers among 2074 unselected Scottish women with the same age distribution.

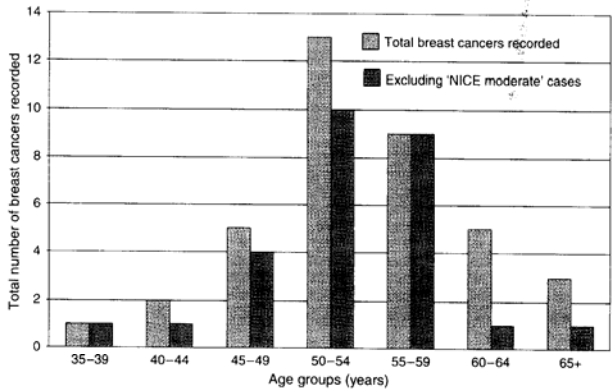

Figure 2 Age distribution of 39 invasive breast cancers recorded up to February 2006 in the study cohort (records incomplete beyond December 2003 so comparison with expected numbers would be invalid).

tumour. Only two ovarian cancers would have been expected but numbers are too small to draw any inference as yet.

DISCUSSION

The overall RR found in this study approached 2.0, appreciably higher than the level of 1.7, which NICE and most other guidelines accept as the threshold above which women should be offered enrolment in a surveillance programme. Given that Cancer Registry data can never be 100% complete since, for example, any cancers occurring in members of our study cohort who had left Scotland would not be recorded, the RR we have calculated is a conservative figure. Furthermore, it is consistent with the findings of the very large reanalysis of epidemiological studies on familial breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2001), which cites a RR of almost two for women with one relative affected between the ages of 40 and 54 years. It is also in keeping with the conclusion of Amir *et al* (2003) that most currently applied algorithms underestimate the RRs associated with 'weak' family histories.

When NICE criteria are applied, 9 of the 28 cancers recorded before the end of the year 2003 were in women at 'moderate' risk. This applies to 12 cancers (in 11 women) from the total series of 39 (30.8%). These potentially 'moderate risk' women thus appear to be over-represented among those who subsequently developed breast cancer, relative to their numbers in the study cohort. If they are excluded, the overall RR falls to 1.32 (95% CI = 0.8–2.1). However, 6 of the 11 NICE 'moderate risk' group were 60 or over at discharge from the cancer family service, whereas women of that age represented less than 10% of our total study population. Elderly people will, of course, have more elderly close relatives and, as breast cancer is an age-related disease, they may have more affected relatives without necessarily implying an increased familial risk.

Different issues arise in relation to the other end of the age spectrum. Where the family history is not strong, the chances of a major gene mutation (BRCA1 or BRCA2) being present are small and so too is the risk of very early-onset breast cancer. The RR in our cohort for women up to the age of 44 years is only 1.05, even if the single 'NICE moderate' patient is included. This age group comprised 45% of our total cohort and, while little weight can be attached to just three cancers, the findings suggest that NICE referral criteria are satisfactory for women under the age of 45 years, that is, the incidence of breast cancer among those who do not 'qualify' for special surveillance through a cancer family clinic is no higher than expected for the general population.

Our findings are most relevant to women aged 45–59 years. They accounted for 46% of our total woman years of follow-up but generated 71% of the breast cancers (84% if the NICE 'moderate risk' cases are excluded), and had a RR of 2.2 (95% CI = 1.4–3.4) or 1.79 (95% CI = 1.00–2.85) with the exclusion. Given that all but 3 of these 27 cancers had actually been diagnosed by the age of 56 years, there is a reasonable expectation that most would have been screen detected in a surveillance programme that provided regular mammography upto the age of 55 years. In fact, 10 of the 13 invasive breast cancers (77%) diagnosed in women from this cohort between the ages of 50 and 52 years were screen-detected, which contrasts with the corresponding figure from ISD of only 41% for the same age group in the unselected Scottish population ($P < 0.02$), suggesting that women who had been discharged from a breast cancer family clinic were particularly motivated to attend for breast screening from the age of 50 years and/or that their tumours were slow growing and hence more amenable to screen detection. NICE criteria include a stipulation that 'moderate' risk means at least a 3% absolute risk of breast cancer between the ages of 40 and 50 years. Restricting analysis to the 1994–2003 cohort, we find that, even excluding the 'NICE moderate' cases, and assuming that half of the cancers detected at the age of 50 or 51 years would have been diagnosed by the age of 50 years in an appropriate screening programme, the cumulative risk over the 5 years from the age of 45 years was 2.3%, whereas the corresponding figure for the 10-year age span 45–55 (with the same assumption that half the cancers diagnosed at the age of 56 years might have been detected by the age of 55 years through screening) is 4.8%. Overall, these findings suggest that, for women aged 45–55 years, family history criteria for inclusion in breast cancer surveillance programmes should be kept under review.

The effect of the breast cancers diagnosed after discharge from the family history clinics would have been to raise the estimated familial risk level for close relatives, in many cases making them eligible for inclusion in regular surveillance programmes. In two instances, where the original family history was of one first-degree relative diagnosed over the age of 40 years, the onset of breast cancer in our patient was followed within 1 year by the same diagnosis in a sister, also at an early age, transforming both families to the upper end of the 'moderate risk' category. Nevertheless, despite the advice on discharge from the cancer family clinics, it was noted that very few of the newly occurring cancers had been reported to the breast cancer family clinics, either by the patients themselves or via the symptomatic breast services.

The practical implications of this study will not necessarily mean an increased workload for breast cancer family history surveillance programmes. While adopting current NICE rather than SIGN criteria means an increase in the proportion of referrals leading to inclusion in a surveillance programme. The actual increase is small since 60–75% of all referred women are already enrolled in special screening. Only 10% of those previously judged to be below threshold risk level (i.e., 2.5–4% of all referrals) will now be added to the surveillance programme. Although that is not a trivial consideration, the added workload (and cost) could be offset if it can be confirmed that many women currently enrolled at the age of 35 or 40 years may safely delay entry until 45 years. For at least some of those at 'moderate', rather than 'high' risk, screening from age 45 to 55 years, perhaps at intervals of 18 rather than 12 months, may prove to be cost-effective and it should be borne in mind that this risk group comprises the bulk of cancer family referrals. Hence, a reduction of some 5% in total workload should be achievable by this approach.

For the present, our findings support the NICE modification of threshold for 'moderate risk' – that is, removing any 'age at diagnosis' restriction where there are two affected close relatives. To extend our findings and to generate evidence that might justify further adjustments to family history criteria for enrolment in special surveillance programmes, we propose to continue follow-up of the cohort of women described in this report, since each additional year provides a further 2000 women years of observation and the incomplete data from 2004 onwards show that accrual of breast cancers is continuing at an undiminished rate.

Longer follow-up may also allow us to address the crucial question of whether special surveillance programmes for women with a family history of breast cancer confer any advantage in terms of outcome. It is impractical to assign such women to a randomised trial, deliberately excluding some from clinical/mammographic screening, but our cohort may generate comparable, albeit more limited, data.

Recent findings in relation to the identification of 'low penetrance' breast cancer susceptibility alleles (Easton *et al*, 2007; Hunter *et al*, 2007) may lead to more precise definition of individual familial risks and it will be of great interest to establish how the distribution of these alleles correlates with breast cancer incidence across a wide spectrum of risk as determined by family history.

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Predicting breast cancer risk: implications of a "weak" family history

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Abstract Published guidelines adopted in many countries recommend that women whose family history of breast cancer places them at a risk ≥1.7 times that of the age-matched general population, should be considered for inclusion in special surveillance programmes. However validation of risk assessment models has been called for as a matter of urgency. The databases of the four Scottish Familial Breast Cancer clinics and the Scottish Cancer Registry have been searched to identify breast cancers occurring among 1,125 women aged 40–56, with family histories placing them below the "moderate" level of genetic risk. The observed incidence over 6 years was compared with age-specific data for the Scottish population. Our findings confirm that when there are two affected relatives (one first degree) the relative risk (RR) exceeds 1.7 regardless of their ages at diagnosis. When only one (first degree) relative was affected at any age from 40 to 55, the RR does not reach 1.7 if that relative was a mother but exceeds it if the relative was a sister. The probable explanation is that sisters are more likely than mother/daughter pairs to share homozygosity for a risk allele. Surveillance programmes might therefore accommodate sisters of women affected before age 55. Evidence that "low penetrance" alleles contributing to breast cancer risk may be recessive should be taken into account in strategies for identifying them.

Keywords Breast cancer · Familial · Recessive genes · Risk

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Background

Family history is a recognised risk factor for breast cancer, absolute and relative risks being influenced by the number of affected relatives, their ages at diagnosis and the closeness of the genetic relationships. Particular note is taken of women

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with a mother or sister diagnosed before age 40 or with bilateral disease. Having more than one close relative with breast cancer and having instances of both breast and ovarian cancer in the family are also regarded as indications of substantially increased risk [20]. Published guidelines recommend that special surveillance programmes, usually incorporating regular mammography with, or without clinical examination, should be offered, from age 35 or 40 to 50 or 55, to women with family histories of this type which place them at "moderate" or "high" risk [10, 11, 14, 19]. The recent NICE (National Institute for Clinical Excellence) guideline [13], defines "moderate" as an age-specific relative risk ≥ 1.7 (compared to the general population) and an absolute risk of $\geq 3\%$ from age 40 to 50. It is recognised that the majority of families with an excess risk of breast cancer do not carry rare mutations in the known high penetrance genes and it is likely that, in most populations, the major genetic contribution to cancer comes from relatively common but lower penetranee variants (Ponder) [17]. However the relationship between family history and future risk of breast cancer remains uncertain, particularly at the lower end of the "moderate" risk spectrum [1, 2] and NICE has declared that "validation of risk assessment models is urgently needed".

The Scottish Breast Cancer Family services operate as a network, with centres based in Aberdeen, Dundee, Edinburgh and Glasgow providing, for the whole population, risk assessment, counselling and, where appropriate, regular prospective surveillance. They are supported by an expert medical genealogy service based in the Information and Statistics Division, NHS Scotland, which has access to the Registrar General for Scotland's records of Births, Marriages and Deaths and to the Scottish Cancer Registry. We have previously published an audit of breast cancer incidence in over 2,000 women referred to any of these Breast Cancer Family clinics but who were judged not to meet family history criteria for "moderate" risk and hence not offered enrolment in a special surveillance programme [2]. With a mean follow-up period of 4 years, 28 invasive breast cancers were recorded, where only 14.4 would have been expected (RR 1.94). Almost one-third of the cancers arose in women with two affected relatives (one first degree) where at least one was ≥ 60 at diagnosis. This is an "exclusion" under SIGN (and several other) guidelines but NICE has removed the age restriction. If these cases (designated "NICE moderate") were discounted, the residual RR fell to 1.32 but it was evident that this figure was not uniform across all age groups. The great majority of the remaining breast cancers observed arose in women aged between 45 and 56, generating a relative risk >1.7. We have therefore extended our analysis of this cohort, to establish whether specific features of family history can identify any further subgroup(s) at significantly increased risk.

Patients and methods

As previously described and with local approval for audit purposes, records of all women referred to any of the four Scottish Breast Cancer Family clinics over the 10-year period from January 1994 to December 2003, but discharged as falling below the "threshold" level of risk for continuing surveillance, were entered onto a secure database. With consent from the Privacy Committee, the Scottish Cancer Registry was then searched to detect any cancers in this cohort. For breast cancers, confirmation and further pathological details were sought from case notes.

The present study is restricted to women who were aged between 40 and 56 years during the period of follow-up for the following reasons.

Our initial analysis demonstrated that the majority of breast cancers recorded in the total cohort occurred in women in the age group 45–56 and that they had by far the highest relative risk. However, if criteria for access to special surveillance are to be modified, revision is likely to involve consideration of close relatives affected from age 40, so it would be unreasonable to delay screening until age 45. We therefore included the 40–45 age group, though anticipating few cancers among them. Most UK guidelines suggest that special surveillance should stop no later than age 55 and that women at moderately increased risk are adequately served by the three yearly National Breast Screening Programme (NBSP) from that point. We had observed, however, that a number of cancers were diagnosed in our cohort at age 56, either presenting symptomatically or detected at mammography. There is a reasonable prospect that these might have been detected if the women had been screened at age 55. Any prediction about the effect of regular surveillance up to age 55 therefore needs to take account of breast cancers currently diagnosed at age 56.

The family history database tabulated affected relatives as mothers, sisters, grandmothers, aunts, cousins and "more distant". It also recorded the age at diagnosis of any affected relative, the number of unaffected sisters and instances of ovarian (and some other) cancers among relatives. Virtually all of this information had been acquired at the time of original risk assessment so that breast cancer incidence in relation to family history was determined prospectively. We could not guarantee that the information provided by the family (usually by means of a standard family history questionnaire) was both complete and accurate in all cases. Indeed gaps and uncertainties were acknowledged in a minority of records. Nevertheless, information about first degree relatives was considered reliable and complete for over 95% of families since the practice of the Scottish clinics, since 1994, has been to allocate specific resources to verification and extension of family histories. Any inaccuracies or gaps in the family data

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were randomly distributed and hence unlikely to introduce any systematic bias into our findings.

There were 1,125 women in the study group (56% of the total cohort) and, following an update on information from the Scottish Cancer Registry in 2007, breast cancers diagnosed up to February 2006 were included in our incidence measurements. The mean period of follow-up (starting from the date of risk assessment and discharge from a family cancer clinic) was thus extended to 6 years.

The expected number of invasive breast cancers for the Scottish population was derived from ISD statistics, taking account of the number of women-years of observation within each 5 year age-group from 40 to 59. The 6 year predicted incidence for an age-matched group of 1,125 women, unselected for family history, was 16.88.

Results

Twenty-nine invasive breast cancers were recorded and confirmed in 27 patients (two women had bilateral synchronous tumours. Both were 50 years old at diagnosis). Six of the cancers occurred in women aged 40–45, 11 in those aged 46–50 and 12 in those aged 51–56. The relative risk (compared to unselected Scottish population figures) for our total group was therefore 1.72. A breakdown of the findings (Table 1, Fig. 1) shows that two distinct subgroups are at substantially higher risk than the remainder. One of these comprises women with two affected close relatives, one or both diagnosed at age 60 or over (the "NICE moderate" group). They comprised 12.1% of the women from our cohort in the 40–56 age range but accounted for six of the 29 breast cancers (20.7%) with a relative risk of 2.94.

The second comprises those with a sister affected at any age between 40 and 55. They constituted 17.6% of the study group but accounted for nine of the 29 breast cancers (31.0%): relative risk 3.02.

If these two subgroups are combined, 15 of the 29 breast cancers (51.7%) are accounted for among just 29.7% of the study population, giving them a relative risk of 2.99, while the remaining 70.3% contributed 14 (48.3%) of the cancers at a relative risk of 1.18. Thus a minority sub-population appears to have been identified, accounting for almost all of the excess risk in the entire cohort.

In striking contrast to the experience of those with an affected sister, having a mother diagnosed with breast cancer at any age above 39 does not confer a relative risk ≥ 1.7. For women with an affected sister or mother, the number of unaffected sisters did not appear to modify absolute or relative risks while, in the absence of an affected first degree relative, having an affected aunt, grandmother or more distant relative did not produce any measurable increase in risk beyond that of the unselected population.

Discussion

This is a relatively small cohort study with, as yet, a limited period of follow-up. Confidence intervals for the relative risks are wide and the only comparison that reaches formal statistical significance is the number of breast cancers recorded for the combined highest risk subgroups ("NICE moderates" plus those with a sister affected aged 40–56) vs. the rest of the cohort. As this result was not predicted in a prior hypothesis it requires corroboration. Nevertheless the excess risk of breast cancer associated with having two affected close relatives (at any age) is well established [7, 15]) and our observation of different degrees of risk associated with an affected sister or mother is consistent with other reports discussed below, though attention has rarely been drawn to it and its potentially important implications may not have been widely recognised. We believe that our data point to recessive inheritance as a major mode of transmission for common determinants of genetic breast cancer risk.

Our study has certain distinctive and advantageous features. First, unlike the great majority of epidemiological investigations on the impact of family history on breast cancer risk, it has a prospective design. Family history was ascertained in detail from women who, at the time, were healthy. They were then followed up to determine the subsequent risk of breast cancer. This eliminates both ascertainment and recall bias that can distort data collected from women who have already been diagnosed with cancer. In addition, the issues of differences in parity and in exposure to environmental cancer risks between mothers and sisters of women with breast cancer, which have also been invoked to explain an apparent excess risk to sisters [3, 15], do not apply when family history is established before diagnosis in the index case—if anything, it ought to generate an excess risk to daughters rather than sisters of affected women because, in simple terms, if the non-genetic causal factors were "weaker" for the mother, the genetic contribution should have been stronger.

The second positive characteristic of our study is the concentration on "weak" family histories, excluding women with relatives affected before age 40 and those with multiple affected close family members. This means that most families carrying mutations in recognised dominant high penetrance "breast cancer" genes (BRCA1, BRCA2, PTEN, p. 53) are eliminated so that the effects of lower penetrance genetic factors should be clearer.

Differences in study design and in the age groups included make direct comparisons with previous reports

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Table 1 1,125 women, aged 40–56, discharged from Tayside "breast cancer family" clinic because they were judged to fall below "SIGN" threshold level of risk for enrolment in surveillance programme

	N (% of all LR women 40–56)	Wm/Yrs F/U	No. of CaBr	CaBr/1,000 Wm/Yrs	RR (95% CI)
Whole cohort	1,125 (100)	6,750	29	4.30	1.72 (1.19–2.46)
"NICE Moderate"	136 (12.1)	816	6	7.35	2.94 (1.2–6.56)
1^{st0} Rel <46	205 (18.2)	1,230	6	4.88	1.95 (0.8–4.36)
Sister <46	80 (7.1)	480	3	6.25	2.50
Mother <46	125 (11.1)	750	3	4.0	1.67
1^{st0} Rel 46–50	163 (14.5)	979	4	4.1	1.63 (0.48–4.36)
Sister 46–50	64 (5.7)	385	3	7.8	3.12
Mother 46–50	99 (8.8)	594	1	1.7	0.67
1^{st0} Rel 51–55	137 (12.2)	824	4	4.85	1.94 (0.56–5.16)
Sister 51–55	54 (4.8)	324	3	9.26	3.70
Mother 51–55	83 (7.4)	500	1	2.0	0.80
1^{st0} Rel >55	198 (17.6)	1,188	5	4.21	1.68 (0.60–4.04)
No 1^{st0} Rel	287 (25.5)	1,722	4	2.32	0.93 (0.28–2.48)
All 1^{st0} Rel <56	505 (44.9)	3,030	14	4.62	1.85 (1.28–2.69)
All sister <56	198 (17.6)	1,189	9	7.57	3.02 (1.52–5.84)
All mother <56	307 (27.3)	1,841	5	2.72	1.09 (0.4–2.6)
NM + sisters <56	334 (29.7)	2,005	15[a]	7.48	2.99 (1.76–5.0)
All others	791 (70.3)	4,746	14[a]	2.90	1.18 (0.68–1.99)

Mean follow-up 6 years (between Jan 1994 and Feb 2006). Total women/years of follow-up 6,750

[a] For difference between these two subgroups $P < 0.02$ (Fischer's exact test)

difficult. However the largest study with a prospective design comparable to our own also records a greater relative risk for sisters than for daughters of affected women [6]. The two largest surveys of publications in this field—a meta-analysis by Paroah and colleagues [15] and the Collaborative group reanalysis [7]—both note that the risk for a sister of an affected woman is higher than that for mother or daughter, at least within age ranges included in the present study. The difference is not statistically significant in either report and in the reanalysis possible reasons are not discussed. Pharoah and colleagues accept the finding as real but attribute it mainly to ascertainment bias and "environmental" factors rather than to the influence of recessive inheritance. In a later publication the same group use data from the Anglian Breast Cancer (ABC) Study to evaluate possible inheritance models for risk of breast cancer presenting before age 55 [3]. They find support for a recessive model with a disease allele frequency of 24% and a penetrance of 42% by age 70. However a polygenic model fits their data equally well, particularly if the effect of mothers' parity is taken into account, as discussed above. Allowance was made in that analysis for known and estimated carriers of BRCA1/2 mutations but cases with very early onset and with multiple affected close relatives were included, so that dominant inheritance may have contributed a greater share of the genetic risk in that cohort than in the present one.

Cui and colleagues [8] argue for a strong recessive effect among Australian breast cancer families and record a much higher cumulative risk for sisters than for mothers of affected probands. However their estimate of disease allele frequency (6.3%) is lower and its penetrance (50% by age 40, close to 100% by age 60) higher than the values suggested by Antoniou and colleagues [3]. Much of the difference may lie in the restriction of the Australian study to probands affected before age 40, implying that substantial proportion of the families were attributable to dominant inheritance. Again, allowance was made for this but the frequency of unidentified mutations in BRCA1 or BRCA2 could only be estimated. The relative contribution of recessive inheritance may have differed from both the ABC study and our own.

In a prospective study of breast cancer where most high penetrance gene effects have been excluded, a higher risk for sisters than daughters of affected women is readily explained by the differing chances of sharing homozygosity at any given locus with mother or sister (Fig. 2). Within the range suggested in the sources cited above for recessive disease allele frequency (6–24%) the chance of a daughter sharing homozygosity with her homozygous mother (genotype of father unknown) is 6–24%, while the corresponding chance of sharing homozygosity with a homozygous sister (both parents being necessarily heterozygous at least) is 28–37%. Extrapolating from our admittedly small dataset, sisters are at almost three times greater risk than daughters and from Fig. 2 this might imply a disease allele frequency of around 10%. Of course, this could be a mean frequency for recessive alleles at two or more independent loci so the overall

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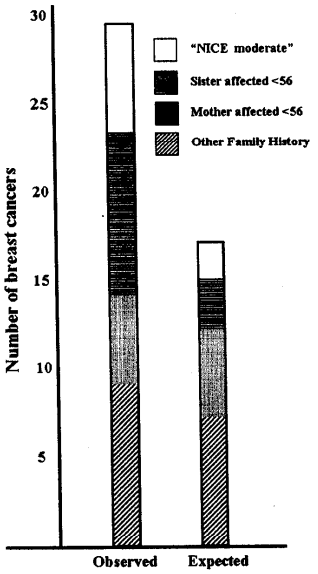

Fig. 1 Distribution of breast cancers observed in our cohort, according to recorded family history, compared to expected numbers calculated from age-matched Scottish population data

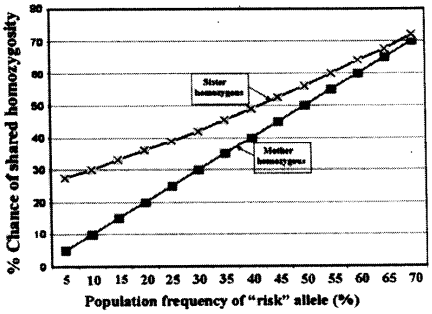

Fig. 2 Probability of shared homozygozity for a putative breast cancer risk allele, according to population frequency of that allele. Sister pairs compared with mother/daughter pairs

contribution of recessive inheritance to breast cancer may be very substantial.

Genome-wide association studies have identified a number of candidate "low penetrance" genes, the most definite being FGFR2, with a disease allele frequency of about 40% and a lifetime penetrance (for homozygotes) approaching 10% [9, 12]). However, none of these candidates appears to behave in a completely recessive manner as heterozygotes have a slightly higher risk for breast than non-carriers. If "low penetrance" alleles at other loci behave in a similar manner, predictions of gene frequency and patient-specific risk, based on epidemiological data, may prove inaccurate.

The present findings carry two potentially important implications. First, in setting family history criteria for enrolment in breast cancer special screening programmes, it may be necessary to consider including women with sisters diagnosed between the ages of 40 and 55. They comprised 17.6% of the women between the ages of 40 and 56 referred to the Scottish Breast Cancer Family clinics and excluded as failing to reach the required risk threshold. That corresponds to less than 3% of all referrals to these clinics, while the "NICE moderate" risk group would add a further 2% to the screening load. In this context it is relevant that we and others have shown investment of resources in extending and verifying reported family histories to reduce the numbers requiring special surveillance by 10–15% [4, 5, 18].

The second conclusion is that, while breast-cancer predisposing variants behaving as Mendelian recessives should eventually be located through genome-wide scans, these involve enormous efforts and a productive alternative first-line strategy might be to search for loci showing an excess of shared homozygosity among sister pairs affected within the age-range 40–55.

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Economic evaluation of a surveillance programme for women with a family history of breast cancer.

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Abstract:

A clinical/mammographic surveillance programme for women at increased genetic risk of breast cancer has operated in Tayside since 1994. Outcome measures – breast cancer detection rates, stage at diagnosis, recurrence rates and survival – have been recorded and compared with data for a consecutive series of young women diagnosed with breast cancer, and for affected young relatives of our index cases. Neither comparison group had been enrolled in any screening programme before age 50. All investigations and treatments have been documented and costed in detail. The findings demonstrate a shift towards earlier stage at diagnosis for cancers among participants in the surveillance programme. This translates into better survival and hence lower cost per Quality Adjusted Life Year (QALY) gained. That measure is particularly sensitive to variations in cancer detection rate and in the extent of beneficial "stage shift" achieved by surveillance but, based on observed values for both, the cost per QALY is less than £4000 while, if highly conservative values are substituted for the sensitive variables, the cost per QALY rises to £12700.

Introduction:

A family history of the disease is recognised as a strong risk factor for breast cancer (Dixon, 2006). Published guidelines recommend that women with multiple affected close relatives or even with one first degree relative affected at an early age (generally under 40) should be offered annual screening by mammography, with or without clinical examination, from around age 35 to age 50 or 55 (Anderson et al, 2008). These guidelines were originally drawn up with only a limited evidence base but, with over ten years experience in many centres, it is now possible to evaluate the benefits and cost-effectiveness of surveillance. This report is based principally on findings from a single clinic serving a population of about half a million, centred on Dundee, in Tayside, Scotland.

Factors that determine cost effectiveness of a clinical service for women with a family history of breast cancer are the number and cost (both financial and psychological) of investigations carried out, the yield of breast cancers detected, the pathological stage of these cancers, the cumulative costs of treatment and the outcomes (recurrence rate and overall survival). The most valid base for comparison would be corresponding costs and outcomes for women with comparable family histories who had not been enrolled in any surveillance programme. However, for ethical and practical reasons it is not possible to randomise such women to “surveillance” or “no surveillance” arms of a controlled trial. Therefore comparisons have been based on published data for Scottish and other populations and on retrospective analysis, first of a consecutive series of Tayside women diagnosed with breast cancer before age 50 (without reference to family history) and second, of young relatives of our index cases who had themselves suffered from breast cancer. Neither comparison group had been enrolled in any screening programme before age 50.

Patients and methods:

In the 11 years since January 1995, 46 breast cancers were diagnosed among 42 women enrolled in the Tayside breast cancer family clinic surveillance programme. Seven of these occurred in women carrying a germ-line mutation in BRCA1 or BRCA2. Mean age at diagnosis was 48 years. For comparison we identified a consecutive series of 40 women diagnosed with breast cancer under the age of 50, in the same clinical centre since 1995 (allowing a minimum of five years follow-up). Pathological stage at presentation and five year recurrence rates were recorded for both groups (Table 1). In addition, from the families of 32 affected patients (excluding BRCA mutation-bearing families) we identified 37 relatives who had been diagnosed with breast cancer under the age of 55 and who had either never had access to pre-symptomatic screening or had been diagnosed at the first (prevalent) round of the National Breast Screening Programme (NBSP). Most of these diagnoses had been recorded at first clinic attendance of our patients, confirmed in the course of family risk assessment and updated by enquiry at subsequent annual clinic visits. Data on outcome were documented for the majority.

Our local findings were also compared with the much larger dataset (442 recorded cancers) compiled from several collaborating European Cancer Family centres, including our own (Moller et al, 1999, 2002, 2007) to confirm that data generated from the limited Tayside series were not unrepresentative.

All procedures carried out in the Breast Cancer Family clinic were tabulated over a 30 month period so that accurate figures for surveillance costs, according to assessed risk level, could be derived (Reis et al, 2006). For each of the above patients in whom breast cancer was diagnosed, all subsequent investigations, surgical and radiotherapeutic procedures, hospital in–patient periods, out-patient clinic visits and drugs used were recorded and detailed unit costs were derived by reference to published UK data (Dewar, 2001), updated and supplemented where necessary by information from the Scottish Health Statistics on Breast Cancer (ISD Scotland "blue book"). Additional details were provided by senior staff of the Finance Department, Ninewells Hospital and Medical School, Dundee and from the Division of Financial Performance Management for NHS Tayside.

Our economic analysis involves the following assumptions, all consistent with the observed data presented below, with recent UK reviews of clinical aspects of breast cancer (Rodger et al, 2006; Smith and Chua, 2006) and with published findings from breast cancer family services elsewhere in the UK and beyond (Gui et al, 2006; Tilanus-Lindhorst et al, 2000; Brekelmans et al, 2001).

1. Within a "family history" surveillance programme, breast cancers arise at a rate of six per thousand annual examinations and 75% are detected at screening.

2. Seventy-seven percent of breast cancers arising in women enrolled in such a screening programme are "early stage" (Path T1/2) and node-negative at diagnosis.

3. Fifty-five percent of breast cancer arising in women under age 50 who have not been enrolled in any screening programme are "early stage" and node-negative.

4. Path stage T1-2 node-negative breast cancer have a 70% probability of complete eradication ("cure") by primary surgery, radiotherapy and, where appropriate, adjuvant chemotherapy.

5. "Late" (node positive) breast cancers have only a 30% probability of complete eradication ("cure") by primary surgery, radiotherapy and adjuvant chemotherapy.

6. Those not "cured" by their primary treatment (30% of "early" and 70% of "late" cases) will require additional treatment and investigations, often involving expensive drugs such as taxanes and/or Herceptin and are likely ultimately to require palliative care.

7. The quality of life (after primary treatment) for "cured" breast cancer patients is good (Casso et al, 2004; Mols et al, 2005; Helgesson et al, 2007) and, for women diagnosed at around 50 years of age, "cure" of breast cancer provides a further 25 years of life (25 QALYs).

Results:

In the 11 year study period, the Tayside "family history" surveillance programme carried out just under 8000 annual screens, comprising clinical examination of the

breasts and two-view mammography. The yield of 46 breast cancers therefore represents a rate of 5.8 per thousand examinations. As shown in table 1a, 34 (74%) were detected at screening and 36 (78.5%) were "early" stage (Path T1-T2, N0). Five year disease-free survival has been 100% for the 29 cases with this length of follow-up. By contrast, for the 40 women (unselected for family history) diagnosed under age 50 who had never been enrolled in a screening programme, only 55% presented at a similarly early stage and overall five year disease-free survival was 82.5%. For the 37 affected relatives of our index cases who had never had access to regular screening, 11 had died from breast cancer within 5 years of diagnosis, 6 more within ten years and only 11 were known to be alive 5 or more years from diagnosis (Table 1b).

Table 2 records the use of resources, with unit and cumulative costs, calculated for "typical" pre-menopausal women diagnosed with either "early" or "late" stage beast cancer. These calculations, make allowance for the different proportions of "early" and "late" breast cancers expected to be "cured" by primary treatment and hence the varying requirement for "second line" drugs, palliative care and other components of management for advanced breast cancer. They demonstrate that the mean cost for an "early" cancer is £24,007, while for a "late" cancer it is £63,672, a difference of £39,665 per patient. Within the "early stage" category, 15% are assumed to be DCIS on the grounds that detection at this "pre-cancerous" stage will prevent later development of invasive cancer, which is, of course, an important purpose of the screening programme (Moller et al, 1999).

Using these cost figures as a base, we then applied the finding that surveillance increases the proportion of "early stage" breast cancers diagnosed in young women from 55% to 77% (Table 1, adjusted slightly downwards by reference to the larger European dataset; Moller et al 2007). Thus, for every hundred breast cancers arising in women enrolled in an annual screening programme, 22 are "transferred" from the poor to the good prognosis category and hence, in cost terms, to the right hand column of Table 2, with a total saving in direct health care costs of £872,630 (22 x £39,665).

It happens that the Tayside "breast cancer family history" service currently undertakes about 1000 screens per year so, from the above figures, the shift to earlier stage at diagnosis of breast cancer would apply to 1.32 women per year (22% of 6 cancers). The saving to the NHS would then be £51,358 (1.32 x £39,665), set against a cost of around £100,000 (@ £100 per screen). Hence the net annual cost of the Tayside programme is £48,642 (£100,000 minus the saving of £51,358). Now if each woman shifted from "late" to "early" stage diagnosis improves her prospects of "cure" by 40% (from 30% to 70%) and "cure" adds 25 years of high quality life (QALYs), the gain is 13.2 QALYs per year (25 x 0.4 x 1.32) at a cost of £3685 per QALY (£48,642 ÷ 13.2).

This does not take into account the fact that many women in their 40's and 50's are in productive employment and/or undertaking important family responsibilities which have an economic value. In practice, therefore, the net cost to the national exchequer is likely to be much less than £3685.

Our calculations are particularly sensitive to variations in two specific parameters, namely the rate of detection of breast cancers in a surveillance programme and the

effectiveness of screening in terms of "shift" to earlier stage at diagnosis. As discussed later, we believe the values we have used are realistic but if more optimistic or pessimistic figures are substituted, as shown in table 3, the cost per QALY can range from £12,700 to less than zero. Even the higher figure is well below the £30,000 attributed to the National Institute for Clinical Excellence, justifying the adoption of new drugs or procedures by the NHS (Appleby et al, 2007).

Discussion:

The costs associated with treatment of breast cancer are not fixed either in time or place. As new drugs emerge, they tend to be increasingly expensive and the indications for their use become ever more circumscribed so that to-day's conclusions may be rapidly superseded. Practices and prices vary from country to country so the figures we have calculated for the UK may not apply precisely elsewhere. Nevertheless, the costs presented in Table 2 are in line with those quoted recently for a US Health care organisation (Anderson et al, 2006) and with an earlier US-based study (Berkowitz et al, 2000), both of which confirm in particular the extremely high cost of palliative care in the terminal phase of the illness.

We have assumed an incidence of 6 breast cancers per year per thousand women in a "family history" surveillance programme, slightly higher than the figure we actually observed but substantially lower than reported elsewhere (Kerilkowske et al, 1995; Kollias et al, 1998; Tilanus-Lindhorst et al, 2000). In the early years of this study, criteria for enrolment in the screening programme were less strictly applied than currently. We and others have found that investment in checking, extending and validating reported family histories substantially alters the distribution of assessed risk and allows better targeting of screening (Campbell et al, 2003; Reis et al, 2006; Brennan et al, 2007). Applying that principle, as we have done since the late 1990's, should increase the cancer incidence rate among those enrolled in surveillance.

The relatively poor prognosis for breast cancer among young women (unscreened and unselected for family history) is well recognised (Chung et al, 1996; Peer et al, 1996) and there is now substantial evidence that pre-menopausal women with a family history of breast cancer, who are enrolled in an annual screening programme, can expect a much better outcome (Robson et al, 2004; Moller et al, 2007) . Our figures of 75% of breast cancers in such women being screen-detected and 77% as small node-negative tumours are conservative in comparison with the recently published experience from one large UK-based clinic (Gui et al, 2006). Five-year disease-free survival is admittedly a rather weak surrogate for long-term "cure" and it can be argued that, by introducing "lead-time bias", the benefits of screening are exaggerated by this measure. Nevertheless, pathological stage, particularly nodal status, is strongly correlated with long-term outcome as well as with extent and cost of primary treatment (Dixon 2006). The marked difference, which we and others (Tilanus-Lindhorst et al, 2000) have confirmed, between screened and unscreened cohorts of young women in this respect is therefore a powerful argument in favour of surveillance, particularly as longer-term follow-up continues to show very high rates of overall and disease-free survival for the screened group (Moller et al, 2007).

It remains to be demonstrated how much of the "gain" is attributable directly to the screening programme. It has been found (Lakhani et al, 2000) that breast cancers

arising in women with a family history of the disease tend to be of lower grade and to carry a better prognosis than sporadic tumours. Follow-up of relevant cohorts have generated conflicting findings (Slattery et al, 1993; Malone et al 1996). The largest and most recent of these found, in the absence of special surveillance, no breast cancer survival advantage for women from "low or moderate" risk families compared to age-matched patients from the general population (Verkooijen et al, 2006). There are also data supporting the view that screening of women under 50 (irrespective of family history) can achieve a stage-shift in breast cancers at diagnosis (Smith, 2000). Our analysis of the outcomes of unscreened affected young relatives of our cohort (with comparable familial risk) suggests that screening has a large beneficial effect. Of course the comparison is far from ideal; some data on the relatives are missing; 23 of them were diagnosed and treated more than 20 years ago, when management and outcomes were generally less satisfactory than to-day; there might be a greater incentive for women whose relatives had died from breast cancer to seek advice about familial risk compared to those whose relatives had survived; lead time bias could generate an apparent survival gain of up to two years without actually changing the outcome. Nevertheless, taking all of these caveats into account, there is a striking disparity between the 10 year survival of 90% recorded in the European multi-centre cohort for mutation-negative women enrolled in annual "family history" surveillance programmes (Moller et al, 2007) and the corresponding figure for our subgroup of unscreened relatives (54%, at best, if all 9 patients with incomplete follow-up information are assumed to remain disease-free).

Carriers of germ-line BRCA1 mutations appear to represent a distinct subgroup that does not benefit from regular screening as currently practised (Robson et al, 2004; Moller et al, 2007). Although introduction of MRI scanning may change this picture, evidence of survival benefit is awaited. Despite detection of their cancers at an apparently early stage (small, node-negative primaries) their recurrence rate is high and in terms of costs and benefits, for the present, they should all be counted in the left hand column of Table 2. Note that this does not apply to BRCA2 mutation-carriers who have a good outcome if screened regularly (Moller et al, 2007). Only some 10% of the Tayside "breast cancer family" clinic patients are thought to carry BRCA mutations, with BRCA1 slightly outnumbering BRCA2 carriers. Five of the 46 observed breast cancers in the screened cohort were known (or later found) to be positive for BRCA1 mutations (and two for BRCA2). Placing all of these 5 in the "late stage" category or removing them entirely from the calculations has only minor effects on the figures presented in tables 2 and 3. However prophylactic surgery (bilateral salpingo-oophorectomy plus bilateral total mastectomy) are not only better options at present for women with known BRCA1 mutations but are also cost effective, given that the total cost of even this extensive surgery is around £11,000 while the "average" cost of management after a breast cancer has been diagnosed is £63,672 (from Table 2). Women carrying BRCA2 mutations are also advised to consider prophylactic salpingo-oophorectomy whch has an NHS cost of less than £3000. The psychological "costs" should not, of course, be ignored or underestimated. Work in this area suggests that, with support, prophylactic surgery is acceptable to many women at high risk (Eisinger et al, 2000; Bebbington-Hatcher and Fallowfield, 2003) but detailed discussion is beyond the scope of this report.

The psychological price of annual screening, with its attendant reminder of breast cancer risk and the anxiety that accompanies the wait for results applies to all women

enrolled in a “family history” surveillance programme. It is difficult to quantify but recent reviews conclude that the impact on general anxiety or cancer-specific worry is broadly neutral (Braithwaite et al, 2004; Hopwood et al, 2004) and it is very clear that women aware of their possible familial risk of breast cancer strongly favour access to regular mammography, regarding its availability as a comfort rather than a source of anxiety (Julian-Reynier et al, 1996; McLeish, 2003).

Previous attempts to calculate the costs and benefits of management options for women at increased genetic risk of breast cancer have been hampered by paucity of objective data. The pioneering 1999 report of Heimdal and colleagues from Norway used standard health insurance charges to measure the costs of screening and assumed a 75% “cure” rate for women who developed breast cancers while taking part in a surveillance programme – not very different from what has subsequently been observed. However they estimated that early diagnosis resulted in 30 added years of life (rather than our figure of 25) and, for simplicity, attributed all of this gain to screening (assuming 100% mortality in the absence of screening). This resulted in a lower cost per life year gained than we have calculated but there is no fundamental conflict between our datasets.

Two Canadian studies undertaken some ten years ago, and an even earlier UK survey, confirm that costs of management of advanced breast cancer are much higher than for early stage disease but all their figures are considerably lower than reported here, reflecting mainly the subsequent introduction of expensive new agents (Richards et al, 1993; Will et al, 2000; Wai et al, 2001).

Griffith and colleagues (2005) carried out a detailed analysis of costs for NHS (UK) cancer genetics services and arrived at figures for QALYs gained through surveillance or prophylactic surgery that, at first sight, appear rather low. However when our own calculations are re-expressed in equivalent terms, it is evident that the two datasets are consistent. Taking our estimate of 13.2 QALYs gained per year (1000 screens), that reduces to 0.013 QALYs per screen and if each woman in the surveillance programme is screened annually for fifteen years, she can expect to gain 0.19 QALYs. However all of the gain is concentrated in the minority of women (around 10%) in the programme who actually develop breast cancer during the period of surveillance. Griffith and colleagues did not attempt to estimate the cost savings achieved through surveillance programmes.

Other published analyses (Schrag et al, 2000; Anderson et al, 2006) have concentrated on carriers of BRCA1 and BRCA2 mutations and, while the advantages of prophylactic surgery (particularly salpingo-oophorectomy) have been emphasised, the important fact that regular surveillance has very different efficacy for BRCA1 compared to BRCA2 mutation-carriers has not been recognised.

In conclusion, while financial considerations are not of prime concern in this area of health care (Moller, 2004), they must be taken into account when decisions are made about commissioning new services or evaluating existing ones (Turner 1999). We believe our detailed, evidence-based analysis of cost-effectiveness of a surveillance programme for women with a family history of breast cancer makes the case for continuing to support this approach.

Table 1. Characteristics of breast cancers in three cohorts of young women.

a)

	"Surveillance" Group	**Unscreened (population)Group**
Number in group	46 (42 patients)	40 (40 patients)
No. (%) screen-detected	34 (74%)	0
No. (%) "Early stage" (T1/2 N0)	36 (78.5%)	22 (55%)
% Disease-free at 5 yrs	Node negative 100% Node positive 100%	Node Negative 92% Node positive 72%

b)

	Relatives of "surveillance" group
Number in group	37
Mean age (Range)	45 yrs (28-54)
Number (%) alive 5yrs from diagnosis	25 (68)
Number (%) alive 10 yrs from diagnosis	11* (29.7)
Number (%) with incomplete information	9** (24.3%)

*** At least 3 died later from breast cancer.**
**** 3 with less than 5 yrs follow-up, 6 no information.**

Table 2.

Unit costs for management of breast cancer in NHS and distribution of costs according to stage at diagnosis.

Component of management and Unit cost	Late stage (T3/4 N+)		Early stage (T1/2 N-)	
	%*	Cost**	%*	Cost**
Initial inpatient stay (5 nights @ £449/nt)	85	£1908	100	£2245
WLE + Ax Surgery, £1673	15	£251	60	£1004
Mx + Ax surgery, £2421	70	£1695	0	£0
Mx + Ax surgery + reconstr, £4513	0	£0	40	£1805
Anthracyclines X 6, £1836	50	£918	60	£1102
FEC x 6, £3155	50	£1577	0	£0
Taxanes, £9160	70	£6412	15	£1374
Herceptin (2 yrs), £44,000	25	£11,000	5	£2200
Bisphosphonates (2 yrs), £4000	50	£2000	10	£400
Tamoxifen (5 yrs), £43	50	£21	50	£21
Radiotherapy (Standard), £1500	100	£1500	60	£900
Palliative radiotherapy, (£400)	70	£280	15	£60
Palliative care in-patient stay (15 nights @£3493), £51,585	70	£36,110	25	£12,896
TOTAL COST	£63,672		£24007	

* Percentage of patients in this category requiring this component

**Cost for a “typical” patient in this category – i.e. unit cost x % requiring it.

WLE = wide local excision; Ax. surgery = axillary surgery; MX = total mastectomy; reconstr = breast reconstruction; FEC = chemotherapy regime using 5-fluorouracil, epirubicin and cyclophosphamide)

Table 3

Effects of changing sensitive parameters (numbers of breast cancers detected per year and percentage of patients who benefit from "stage shift" of their cancer) on cost-effectiveness of surveillance programmes.

No.Breast Cancers diagnosed/yr	% shift to "curable" stage	No. Ca Br Patients benefiting/yr	QALYs gained*	Annual saving £**	Annual net cost £***	Cost per QALY £
6	22	1.32	13.2	51,358	48,642	3685
4	22	0.88	8.8	34,905	65,095	7396
9	22	1.98	19.8	78,537	21,463	1084
6	15	0.9	9	35,669	64,301	7145
6	30	1.8	18	71,398	28,601	1589
4	15	0.6	6	23,799	76,201	12,700
4	30	1.2	12	47,598	52,402	4367
9	15	1.35	13.5	53,548	46,452	3433
9	30	2.7	27	107,096	-7096	-263

***Assumes 10 QALYs per additional patient detected at a "curable" stage.**
**** Assumes saving of £39,665 per additional patient detected at "curable" stage (from Table 2).**
***** Assumes fixed annual screening cost of £100,000 (for 1000 women screened)**

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Appendix B

Clinic letters

Acute Services Division

Clinical Genetics, Human Genetics Unit
Clinical Group of Surgery & Oncology
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

«Title» «Prename» «Surname»
«Address»
«Area»
«Town» «Postcode»

Date Typed
Our Ref CHI «Date_of_birth» «MPI»
Pedigree No «Pedigree_No»
Enquiries to 01382 632035

Dear «Title» «Surname»

We have been asked to advise you regarding your family history of cancer. Most cancers are not hereditary but there are rare hereditary forms of the condition. I would be most grateful if you would complete and return the enclosed form providing us with details of your family history. This will enable us to determine if you have relatives that are likely to have had hereditary cancer and if you are at increased risk from the condition.

We will write to you and your family doctor as soon as we have evaluated your family history. We will arrange a genetics clinic appointment for you if your history indicates that you might benefit from additional screening for early signs of the condition or if we may be able to modify our estimate of your risk with genetic tests. Please contact us if you are unable to complete the family history questionnaire, as we will not make a clinic appointment for you if we have not received a completed questionnaire or confirmation that you want a clinic appointment.

If you have any queries regarding the information we are requesting please don't hesitate to phone 01382 632035 and ask to speak to one of the Genetic Counsellors.

We look forward to hearing from you.

Yours sincerely

Signed electronically

David R Goudie
Consultant Clinical Geneticist

Enc: Family History Clinic Form + FREEPOST envelope

cc: Registry

If you do not return your completed questionnaire or contact us you may not receive a clinic appointment

FHBCques

Dorothy Young, Genetics Associate, Clinical Genetics,
Pathology Department, Ninewells Hospital, Dundee, DD1 9SY
Tel: 01382 496369 Fax: 01382 494382 E-mail:
dorothy.young@tuht.scot.nhs.uk

Please quote ref. no. **«Pedigree_No»**

17 June, 2008

«Title» «Prename» «Surname»
«Address»
«Area»
«Town»
«Postcode»

Dear «Title» «Surname»

You kindly agreed to participate in our Family History Breast Cancer clinic study. Our aim was to improve the service we provide. We would like to show whether women would prefer to attend a clinic to discuss their risk or are happy with a letter. Some women with a similar risk to your own were seen at our clinic while others received a letter. We are comparing their satisfaction with our service.

We would be grateful if you could complete the enclosed questionnaire and return it in the prepaid envelope. This information will be used to assess the service we offered you and may be used to determine future service provision.

Information will only be used in relation to this study and will be confidential.

Please contact me on 01382 496369 if you have any questions or concerns.

Thank you.

Yours sincerely

Dorothy Young
Genetic Associate

Enc. Breast Cancer Family History Project Questionnaire
Prepaid envelope

Acute Services Division

Clinical Genetics, Human Genetics Unit
Clinical Group of Surgery & Oncology
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

«Title» «Prename» «Surname»
«Address»
«Area»
«Town» «Postcode»

Date Typed
Our Ref CHI «Date_of_birth» «MPI»
Pedigree No «Pedigree_No»
Enquiries to 01382 632035

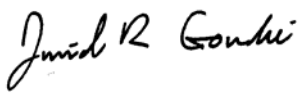
Dear «Title» «Surname»

We have been asked to advise you regarding your family history of cancer. Most cancers are not hereditary but there are rare hereditary forms of the condition. I would be most grateful if you would complete and return the enclosed form providing us with details of your family history. Our secretaries will arrange a clinic appointment for you and this will be sent to you nearer the time of your appointment.

If you have any queries regarding the information we are requesting please don't hesitate to phone 01382 632035 and ask to speak to one of the Genetic Counsellors.

We look forward to hearing from you.

Yours sincerely



Signed electronically

David R Goudie
Consultant Clinical Geneticist

Enc Family History Clinic Form + FREEPOST envelope

cc Registry

FOR OFFICE USE ONLY
Date received:

«Pedigree_No»
Our ref no

FAMILY HISTORY CLINIC

Clinical Genetics, Department of Pathology, Ninewells Hospital
Dundee DD1 9SY (tel 01382 632035)

Your full name: **«Prename» «Surname»**
Address: **«Address»**
«Area»
«Town»
«Postcode»

Maiden name: ……
Any previous names: ……

Telephone number: ……

Date of birth: **«Date_of_birth»**

Place of birth: ……

Please check the details given above and correct if necessary.

Have any of your relatives attended our genetics clinics?

If yes please give name & date of birth of relative……

NOTE:
The following tables ask for information about your family please complete these tables as far as you are able to. The first table is asking for information about your relatives who have had a cancer, it is essential for us to have as much information as you can give us, if you don't know something and are unable to find out please write 'don't know'. If someone has had more than one cancer please tell us. The next tables are asking for information about all of your relatives. Information about how people are related to each other, their ages (or their age when they died if they are deceased) are all important in the interpretation of your family history. Please give us as much information if you can and let us know if it incomplete.

FHBCQREM

Dorothy Young, Genetics Associate, Clinical Genetics,
Pathology Department, Ninewells Hospital, Dundee, DD1 9SY
Tel: 01382 496369 Fax: 01382 494382 E-mail: dorothy.young@tuht.scot.nhs.uk

Please quote ref. no. **«Pedigree_No»**

8 November, 2006

«Title» «Prename» «Surname»
«Address»
«Area»
«Town»
«Postcode»

Dear «Title» «Surname»

You kindly agreed to participate in our Family History Breast Cancer clinic study. For completion of this study it would be very helpful if you could return the questionnaire we recently sent you.

Information will only be used in relation to this study and will be confidential.

Please contact me on 01382 496369 if you have any questions or concerns.

Thank you.

Yours sincerely

Dorothy Young
Genetic Associate

MANAGEMENT SUMMARY (FHBC ave)

Date printed: 08 November 2006

Name: **«Prename» «Surname»** Ref. no. **«Pedigree_No»**
CHI **«Date_of_birth» «MPI»**
Address: **«Address» «Area» «Town» «Postcode»**
Tel: **«Telephone»**
GP: **«Clinician_Name» «Address_1» «Address_2» «Address_3» «Address_4»**

RISK ASSESSEMENT

CONFIRMATION OF CASES (please specify- Pathology, Cancer registry, Death Certificate (Alison, MRC Registry), Hospital Notes, Oncology)

……Time spent……
……Time spent……
……Time spent……
……Time spent……

OR

Comment if no confirmations ……

Risk altered after confirmations of cancers YES / NO

Cyrillic Risk: «Heterozygote_risk»

Action:

☐ odd Appointment (clinic- area 5 Tues,am): Date:……. Time:…….
☐ attended : time taken:……
☐ cancelled/DNA next appt:……..

☐ even Letter to patient and GP Date sent:…….

Please give details if assessed risk is changed either at appointment / after letter……
……..

Comments……
……..
……..

Clinical Genetics
Human Genetics Unit
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

«Clinician_Name»
«Source_Name»
«Address_1»
«Address_2»
«Address_3»
«Address_4»

Date Typed
Date Dictated
Your Ref
Our Ref DRG/sb «Date_of_birth» «MPI»
Pedigree No **«Pedigree_No»**
Enquiries to Dr David Goudie
Extension 32135
Direct Line (01382) 632151
Email david.r.goudie@tuht.scot.nhs.uk

Dear Dr «ClinicianSurname»

Re: «Prename» «NamesSurname», DOB «Date_of_birth», «Address», «Area», «Town», «Postcode»

You referred this patient to the genetics clinic at Ninewells Hospital for assessment of their risk from familial cancer. We have sent them a questionnaire to complete providing us with details of their family history on two occasions and given them the option of contacting us directly to confirm that they would like a genetics clinic appointment. They have not returned the questionnaires or contacted us to confirm that they would like an appointment.

We have not arranged a clinic appointment for them. Please re-refer them if they would like an appointment.

Yours sincerely,

David R Goudie

David R Goudie
Consultant in Clinical Genetics

c.c. Registry
Casenotes

Clinical Genetics
Human Genetics Unit
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

«Title»«Prename»«Surname»
«Address»
«Area»
«Town»
«Postcode»

Date Typed
Date Dictated
Date of Clinic
Your Ref
Our Ref DY/«Date_of_birth» «MPI»
Family No «Pedigree_No»
Enquiries to Genetic Counsellors
Telephone (01382) 632035

Dear «Title» «Surname»

I am sorry that you could not attend your recent appointment at the Family History Breast Cancer clinic on. As you have failed to attend we are unable to arrange another appointment for you. You should ask your GP to refer you back to this clinic and we will put you back on our waiting list.

Please do not hesitate to contact us on 01382 632035 if you have any questions or concerns.

Yours sincerely

Dorothy Young
Genetic Associate

cc. «Clinician_Name» «Source_Name» «Address_1» «Address_2» «Address_3» «Address_4»
Registry
Case notes

Clinical Genetics
Human Genetics Unit
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

«Clinician_Name»
«Source_Name»
«Address_1»
«Address_2»
«Address_3»
«Address_4»

Date Typed
Date Dictated
Date of Clinic
Your Ref
Our Ref DY/«Date_of_birth» «MPI»
Family No «Pedigree_No»
Enquiries to Dorothy Young, Genetic Associate
Extension 36369
Telephone (01382) 632035

Dear «Clinician_Name»

RE: «Title» «Prename» «Surname» («Date_of_birth» «MPI») «Address» «Area» «Town» «Postcode»

«Title» «Surname» has failed to attend the Family History Breast Cancer Clinic on«Pedigree_No». We have not organised any further appointments for her. I have enclosed a letter sent to her.

However if she has moved address or out of the area please could you let us know.

Thanks.

Yours sincerely

Dorothy Young PhD

Genetic Associate

Enc.

cc. Registry
Casenotes

Tayside University Hospitals

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Ninewells Hospital & Medical School
Dundee
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Your Ref	
Our Ref	/sm/jr/«Date_of_birth» «MPI»
Family No	«Pedigree_No»
Enquiries to	
Extension	
Direct Line	(01382)
Email	david.r.goudie@tuht.scot.nhs.uk

Dear «Title» «Surname»

We have been asked to assess your risk from cancer because of your family history of the condition. Thank you for providing us with details of your family history.

Most breast cancer is not hereditary but some women with breast cancer have a hereditary form of the condition. Women with hereditary breast cancer usually have close relatives that are affected at unusually early ages.

The information that we have about your family history indicates that it is unlikely that a genetic fault causing breast cancer is present in your family. Your own risk of developing breast cancer is not significantly increased compared to the risk for other women of your age. It is therefore unlikely that you would benefit from additional screening for early signs of breast cancer at present if you have no breast symptoms.

Although your risk from breast cancer is not significantly increased all women are at some risk from the condition. Should you develop breast symptoms that you are concerned about you should seek medical advice. You should ensure that you are enrolled in the National Breast Screening Program once you are eligible aged 50. There is evidence that regular screening for early signs of breast cancer is of benefit for women over 50 years of age.

We have not arranged a clinic appointment for you at the breast cancer family history clinic but please do not hesitate to contact us if you have any other questions or if other members of your family develop cancer which might alter our estimate of your own risk.

Yours sincerely

Lorna McLeish
Genetic Nurse Specialist

David R Goudie
Consultant Clinical Geneticist

cc ADD REFERRING CLINICIAN (if diff. to GP)
«Clinician_Name» «Source_Name» «Address_1» «Address_2» «Address_3» «Address_4»
Registry File
Case Notes

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Enquiries to	Dr D Goudie
Extension	32035
Direct Line	(01382) 632035
Email	david.r.goudie@tuht.scot.nhs.uk

Dear «Title» «Surname»

We have been asked to assess your risk from cancer because of your family history of the condition. Thank you for providing us with details of your family history.

Most breast cancer is not hereditary but some women with breast cancer have a hereditary form of the condition. Women with hereditary breast cancer usually have close relatives that are affected at unusually early ages.

Although it is possible that some of your relatives have had hereditary breast cancer, as you get older without developing the condition, the risk that you have a hereditary tendency to develop cancer diminishes. You are already eligible for breast screening through the National Breast Screening Program and so we have not arranged for you to have screening through the Family History Breast Cancer clinic. You should ensure that you are enrolled in the National Breast Screening Program as you are now eligible. There is evidence that regular screening for early signs of breast cancer is of benefit for women over 50 years of age.

Gene testing is only possible in a minority of families with breast cancer. Identifiable faults in the breast cancer genes are infrequently found in families where less than four women have had breast cancer. It is unlikely that genetic tests would alter our estimate of your risk from breast cancer.

Although we have not arranged a clinic appointment for you should seek medical advice if you develop breast symptoms that you are concerned about. Please do not hesitate to contact us if you have any other questions or if other members of your family develop cancer which might alter our estimate of your own risk.

Yours sincerely

Yours sincerely

Lorna McLeish
Genetic Nurse Specialist

David R Goudie
Consultant Clinical Geneticist

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Family No **«Pedigree_No»**
Enquiries to Dorothy Young, Genetic Associate
Extension 36369
Direct Line (01382) 496369
Email dorothy.young@tuht.scot.nhs.uk

Dear «Title» «Surname»

Thank you for agreeing to participate in our Family History Breast Cancer study and for completing the form with details of your family history. Your risk of developing breast cancer has been assessed and it is not significantly increased compared to other women your age.

Most breast cancer is not hereditary but some women with breast cancer have a hereditary form of the condition. Women with hereditary breast cancer usually have close relatives that are affected and the hereditary forms of the condition tend to occur at unusually early ages.

INSERT FAMILY HISTORY DETAILS. RATIONAL FOR RISK. It is therefore unlikely that you would benefit from additional screening for early signs of breast cancer at present if you have no breast symptoms.

Although your risk from breast cancer is not significantly increased all women are at some risk from the condition. Should you develop breast symptoms that you are concerned about you should seek medical advice (symptoms you should look out for are described in the enclosed Tayside Breast Aware Leaflet). You should ensure that your are enrolled in the National Breast Screening Program as you are now eligible. There is evidence that regular screening for early signs of breast cancer is of benefit for women over 50 years of age.

Gene testing is only possible in a minority of families with breast cancer. Identifiable faults in the breast cancer genes are infrequently found in families where less than four women have had breast cancer. It is unlikely that genetic tests would alter our estimate of your risk from breast cancer.

We have not arranged an appointment for you at the Family History Breast Cancer clinic but please do not hesitate to contact us if you have any other questions or if other members of your family develop cancer which might alter our estimate of your own risk.

Yours sincerely

Dorothy Young
Genetic Associate

Yours sincerely

David R Goudie
Consultant Clinical Geneticist

cc ADD REFERRING CLINICIAN (if diff. to GP)
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Enquiries to Dorothy Young, Genetic Associate
Extension 36369
Direct Line (01382) 496369
Email dorothy.young@tuht.scot.nhs.uk

Dear «Clinician_Name»

RE: «Title» «Prename» «Surname» («Date_of_birth» «MPI»)
«Address» «Area» «Town» «Postcode»

«Prename» «Surname» completed a detailed family history questionnaire and we have assessed her risk of developing breast cancer. Women found to have a low risk of developing breast cancer that have agreed to participate in our study were randomised either to receive a letter or an appointment to one of our genetics clinics. I have enclosed a copy of an information leaflet and of our letter to «Prename» «Surname» explaining her risk from breast cancer. She was not given an appointment for our genetics clinic.

INSERT FAMILY HISTORY. Fortunately her risk is not significantly increased. We have not arranged for her to have mammogram or a clinical examination of breasts.

If «Prename» «Surname» or yourself have any further questions or concerns please do not hesitate to contact us at the above address or telephone me on 01382 496369.

Yours sincerely

Yours sincerely

Dorothy Young
Genetic Associate

David R Goudie
Consultant Clinical Geneticist

Enc Patient Information Sheet
Signed Consent Form

c.c. ADD GP if diff. from REFERRING CLINICIAN (if diff. to GP)
Registry
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Family No «Pedigree_No»
Enquiries to
Extension
Direct Line (01382)
Email david.r.goudie@tuht.scot.nhs.uk

Dear «Title» «Surname»

Most breast cancer is not hereditary but some women with breast cancer have a hereditary form of the condition. Women with hereditary breast cancer usually have close relatives that are affected and the hereditary forms of the condition tend to occur at unusually early ages.

Fortunately investigation of your family history indicates that it is unlikely that a genetic fault causing breast cancer is present in your family. Your own risk of developing breast cancer is not significantly increased compared to the risk for other women of your age. It is therefore unlikely that you would benefit from additional screening for early signs of breast cancer at present if you have no breast symptoms.

Although your risk from breast cancer is not significantly increased all women are at some risk from the condition. Should you develop breast symptoms that you are concerned about you should seek medical advice. You should ensure that you are enrolled in the National Breast Screening Program once you are eligible aged 50. There is evidence that regular screening for early signs of breast cancer is of benefit for women over 50 years of age.

We have not arranged another appointment for you at the breast cancer family history clinic but please do not hesitate to contact us if you have any other questions or if other members of your family develop cancer which might alter our estimate of your own risk.

Yours sincerely

Lorna McLeish
Genetic Nurse Specialist

David R Goudie
Consultant Clinical Geneticist

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Family No **«Pedigree_No»**
Enquiries to Dorothy Young, Genetic Associate
Extension 36369
Direct Line (01382) 496369
Email dorothy.young@tuht.scot.nhs.uk

Dear «Title» «Surname»

It was a pleasure to meet you at our genetics clinic. Thank you for agreeing to participate in our Family History Breast Cancer study and for completing the form with details of your family history.

Most breast cancer is not hereditary but some women with breast cancer have a hereditary form of the condition. Women with hereditary breast cancer usually have close relatives that are affected and the hereditary forms of the condition tend to occur at unusually early ages.

Fortunately investigation of your family history indicates that it is unlikely that a genetic fault causing breast cancer is present in your family. Your own risk of developing breast cancer is not significantly increased compared to the risk for other women of your age. It is therefore unlikely that you would benefit from additional screening for early signs of breast cancer at present if you have no breast symptoms.

Although your risk from breast cancer is not significantly increased all women are at some risk from the condition. Should you develop breast symptoms that you are concerned about you should seek medical advice. You should ensure that your are enrolled in the National Breast Screening Program as you are now eligible. There is evidence that regular screening for early signs of breast cancer is of benefit for women over 50 years of age.

Gene testing is only possible in a minority of families with breast cancer. Identifiable faults in the breast cancer genes are infrequently found in families where less than four women have had breast cancer. It is unlikely that genetic tests would alter our estimate of your risk from breast cancer.

We have not arranged another appointment for you. Please do not hesitate to contact us if you have any other questions or if other members of your family develop cancer which might alter our estimate of your own risk.

Yours sincerely

Dorothy Young
Genetic Associate

Yours sincerely

David R Goudie
Consultant Clinical Geneticist

cc ADD REFERRING CLINICIAN (if diff. to GP)
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Family No **«Pedigree_No»**
Enquiries to Dorothy Young, Genetic Associate
Extension 36369
Direct Line (01382) 496369
Email dorothy.young@tuht.scot.nhs.uk

Dear «Clinician_Name»

RE: «Prename» «Surname» («Date_of_birth» «MPI»)
«Address» «Area» «Town» «Postcode»

«Title» «Surname» completed a detailed family history questionnaire and we have assessed her risk of developing breast cancer. Women found to have a low risk of developing breast cancer that have agreed to participate in our study were randomised either to receive a letter or an appointment to one of our genetics clinics. «Title» «Surname» was seen at our genetics clinics to discuss her risk of breast cancer (a copy of the summary letter sent to her is enclosed with a copy of patient information sheet and her signed consent form).

INSERT FAMILY HISTORY. Fortunately her risk is not significantly increased. We have not arranged for her to have a mammogram or clinical examination.

If «Title» «Surname» or yourself have any further questions or concerns please do not hesitate to contact us at the above address or telephone me on 01382 496369.

Yours sincerely

Yours sincerely

Dorothy Young
Genetic Associate

David R Goudie
Consultant Clinical Geneticist

Enc Patient Information Sheet
Copy Signed Consent Form

c.c. ADD GP if diff. from REFERRING CLINICIAN (if diff. to GP)
Registry
Casenotes

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Date Dictated
Date of Clinic
Your Ref
Our Ref /sm/jr/ «Date_of_birth» «MPI»
Family No «Pedigree_No»
Enquiries to
Extension
Direct Line (01382)

Dear «Title» «Surname»

Most breast cancer is not hereditary but some women with breast cancer have a hereditary form of the condition. Women with hereditary breast cancer usually have close relatives that are affected and the hereditary forms of the condition tend to occur at unusually early ages.

The hereditary forms of breast cancer are caused by faults in genes (hereditary instructions) that normally tell the body how to make substances that protect against cancer. In some families the same genetic faults are associated with an increased risk from both breast cancer and cancer of the ovaries. We all inherit two copies of most genes. We inherit one copy from our mother and a second from our father. A woman with hereditary breast cancer has one normal and one faulty copy of one of the breast cancer genes. When she has children she can pass either her normal or her faulty copy of the gene on to each of her children. A daughter inheriting normal copies of the breast cancer genes from both of her parents will not have an increased risk from breast cancer and cannot pass the predisposition on to her children. A daughter inheriting a faulty copy of the gene will have an increased risk of breast cancer but not all gene carriers will develop the condition.

It is possible that some of your relatives have a hereditary form of breast cancer. The majority of women with a family history like you will not develop cancer but your risks are higher than average.

Early detection and treatment of breast cancer can improve the chance of successful treatment. We will arrange to see you each year at the Family History Breast Cancer Clinic to screen for early signs of the condition.

In some families we can identify the precise genetic fault causing breast cancer using blood samples from surviving affected women. In families where a specific genetic fault has been identified we can test other family members to determine if they have inherited the faulty gene. /

«Title» «Prename» «Surname»

As you get older without developing breast cancer it becomes progressively less likely that you have inherited a faulty breast cancer gene. Unless you develop the condition yourself your daughters' risk will not be sufficiently increased for them to be likely to benefit from screening for early signs of the condition before they are 50 years old, unless they have breast symptoms. Even in families with hereditary breast cancer it is rare for the condition to affect women before they are in their 30s.

cc ADD REFERING CLINICIAN (if diff. to GP)
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Our Ref	/sm/jr/ «Date_of_birth» «MPI»
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Enquiries to	Dr D Goudie
Extension	32035
Direct Line	(01382) 632035
Email	david.r.goudie@tuht.scot.nhs.uk

Dear «Title» «Surname»

Most breast cancer is not hereditary but some women with breast cancer have a hereditary form of the condition. Women with hereditary breast cancer usually have close relatives that are affected and the hereditary forms of the condition tend to occur at unusually early ages.

Although it is possible that some of your relatives have had hereditary breast cancer, as you get older without developing the condition, the risk that you have a hereditary tendency to develop cancer diminishes. You are already eligible for breast screening through the National Breast Screening Program so we have not arranged for you to have screening through the Family History Breast Cancer clinic. You should ensure that your are enrolled in the National Breast Screening Program as you are now eligible. There is evidence that regular screening for early signs of breast cancer is of benefit for women over 50 years of age.

Gene testing is only possible in a minority of families with breast cancer. Identifiable faults in the breast cancer genes are infrequently found in families where less than four women have had breast cancer. It is unlikely that genetic tests would alter our estimate of your risk from breast cancer.

We have not arranged another appointment for you. Should you develop breast symptoms that you are concerned about you should seek medical advice. Please do not hesitate to contact us if you have any other questions or if other members of your family develop cancer which might alter our estimate of your own risk.

Yours sincerely

Lorna McLeish
Genetic Nurse Specialist

Yours sincerely

David R Goudie
Consultant Clinical Geneticist

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Date Typed
Date Dictated
Date of Clinic
Your Ref
Our Ref «Date_of_birth» «MPI»
Family No «Pedigree_No»
Enquiries to Genetic Counsellor / Dr D Goudie
Direct Line (01382) 632035

Dear «Title» «Surname»

I am sorry that you could not attend for your recent appointment at the Family History Breast Cancer clinic. We have not arranged another appointment for you. Please ask your family doctor to re-refer you if you would like another clinic appointment.

Yours sincerely

Genetic Counsellor

dd. «Clinician_Name» «Source_Name» «Address_1» «Address_2» «Address_3» «Address_4»
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Our Ref «Date_of_birth» «MPI»
Family No «Pedigree_No»
Enquiries to Genetic Counsellor
Extension 362035
Telephone (01382) 632035

Dear «Clinician_Name»

«Title» «Prename» «Surname» («Date_of_birth» «MPI») «Address» «Area» «Town» «Postcode»

«Title» «Surname» has failed to attend for her appointment at the Family History Breast Cancer Clinic. We have not organised any further appointments but we would be happy to see her again if you wish to re-refer her.

Yours sincerely

Genetic Counsellor

Enc Copy of letter to «Prename» «Surname»

Cc Dr Marta Reis, Associate Specialist, Breast Office, Ward 10, Ninewells Hospital
Registry
Casenotes

Clinical Genetics
Human Genetics Unit
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

«Clinician_Name»
«Address_1»
«Address_2»
«Address_3»
«Address_4»

Date Typed	21st June 2005
Our Ref	DY/«Date_of_birth» «MPI»
Family No	«Pedigree_No»
Enquiries to	Dorothy Young
Extension	36369
Direct Line	(01382) 496369
Email	dorothy.young@tuht.scot.nhs.uk

Dear «Clinician_Name»

Thank you for participating in the Tayside study of breast cancer genetic service organisation. As you know, over the past 3 years we have assessed the acceptability of a triage system for women referred to the service, whereby risk of breast cancer is judged to be “low”, “moderate” or “high”, after construction and verification of a detailed family history. Women at moderate or high risk or who did not return their family history questionnaire were given appointments to the Friday multidisciplinary counselling/screening clinic. Women assessed at low risk during the study were randomised to either receive a letter explaining that they would not be enrolled in a special screening programme or were given the same information through a personal interview with a genetics nurse specialist or genetics associate. We greatly appreciate the views of GPs on these approaches and will be grateful if you can spare a few minutes to complete and return this short questionnaire in the FREEPOST envelope provided.

The questions relate specifically to women who consented to be randomised, were found to be at low genetic risk, and who were told this by letter or interview. They do not refer to women who attended the surveillance clinic even if they were subsequently found to be at low risk and discharged.

«Prename» «Surname» participated in our Family History Breast cancer study. I have enclosed a copy of the study information sheet. She was assessed from her family history questionnaire to be at low risk of hereditary breast cancer. As part of the study she was randomised to receive a letter to inform her of her risk.

Please can you complete the short questionnaire and return it in the FREEPOST envelope. This will help assess how the study has affected your clinical workload.

Yours sincerely

Dorothy Young
Genetic Counsellor

Enc.

c.c. registry

Appendix C

Patient questionnaire

Your personal code no ..... Date Issued ..... (For office use only)

BREAST CANCER FAMILY HISTORY PROJECT QUESTIONNAIRE

Thank you for filling in our questionnaire. Most of the questions just require you to tick a box, but feel free to write alongside any of the questions or continue on a separate sheet of paper if you wish. The questionnaire should take about half-an-hour to complete. Please read the instructions for each question carefully. There are questions on both sides of each page. We would be glad if you could complete all of the questions, since it is important that we have full information from you. When you have completed the questionnaire, please check to make sure you have not missed anything out, and then return it to is in the stamped addressed envelope provided. We look forward to hearing from you soon.

Please fill in:

Your surname/family name .....

Your forename(s) .....

Today's date ..... | ..... | .....
day **month** **year**

Please let us know if you have had a change of address or telephone number (write "none" if there has been no change).

_____

_____

_____

_____

CONCERNS ABOUT BREAST CANCER

Most of us have concerns about our health. The following questions ask about any concerns you may have regarding breast cancer. For each question, please tick one box to indicate your answer.

1. During the past month, how often have you thought about your own chances of developing breast cancer? Would you say....
   - Not at all or rarely ☐
   - Sometimes ☐
   - Often ☐
   - Almost all of the time ☐

2. During the past month, have thoughts about your chances of getting breast cancer affected your mood? Would you say....
   - Not at all or rarely ☐
   - Sometimes ☐
   - Often ☐
   - Almost all of the time ☐

3. During the past month, have thoughts about your chances of getting breast cancer affected your ability to perform daily activities? Would you say....
   - Not at all or rarely ☐
   - Sometimes ☐
   - Often ☐
   - Almost all of the time ☐

4. How concerned are you about the possibility that you might get breast cancer some day? Would you say...
   - Not at all ☐
   - Somewhat ☐
   - Moderately ☐
   - Very concerned ☐

5. How often do you worry about cancer? Would you say....
   - Not at all ☐
   - Occasionally ☐
   - Frequently ☐
   - Constantly ☐

6. How much of a problem is worrying about breast cancer to you? Would you say...
   - Not at all ☐
   - Somewhat ☐
   - Definitely ☐
   - Severe problem ☐

YOUR EXPERIENCES SINCE RECEIVING YOUR RISK ASSESSMENT

Since you received your risk assessment how often have you experienced the following things because of thoughts and feelings about breast cancer?

Please read each statement carefully and circle one number after each statement.

(0 = 'Not at all'; 1 = 'Rarely'; 2 ='Some of the time'; 3 = ''Quite a lot of the time')

Remember there are no right or wrong answers.

	Not at all	*Rarely*	*Some of the time*	*Quite a lot of the time*
Had trouble sleeping	0	1	2	3
Experienced a change in appetite	0	1	2	3
Been unhappy or depressed	0	1	2	3
Been scared and panicky	0	1	2	3
Felt nervous or strung-up	0	1	2	3
Felt under strain	0	1	2	3
Found you have been keeping things from those who are close to you	0	1	2	3
Found yourself taking things out on other people	0	1	2	3
Found yourself noticeably withdrawing from those who are close to you	0	1	2	3
Had difficulty doing things around the house which you normally do	0	1	2	3
Had difficulty meeting work or other commitments	0	1	2	3
Felt worried about your future	0	1	2	3

All things considered would you say your experiences since referral for genetic assessment have caused any of the following? Please read each statement carefully and circle one number after each statement.
(0 = 'Not at all'; 1 = 'A little bit'; 2 ='Quite a bit'; 3 = 'A great deal').

	Not at all	*A little bit*	*Quite a bit*	*A great deal*
A sense of reassurance that you do not have breast cancer	0	1	2	3
Feeling more relaxed	0	1	2	3
Improved relationships with friends or relatives	0	1	2	3
Feeling more able to do things which you normally do	0	1	2	3
Feeling more able to meet your home and/or work responsibilities	0	1	2	3
Feeling more hopeful about the future	0	1	2	3
Feeling less anxious about breast cancer	0	1	2	3
Getting on better with those around you	0	1	2	3
Been sleeping better	0	1	2	3
A greater sense of well-being	0	1	2	3

RISK OF BREAST CANCER

Now that you have received your risk assessment, we would like to ask you a few questions regarding how you feel about your risk for breast cancer. Please read carefully each of the following questions, and tick the statement which best applies to you. Remember there are no right or wrong answers.

1) What prompted you to seek assessment? _____

_____

2) What were you told was your risk of developing breast cancer during your lifetime?

Please write here _____

_____

3) What level of risk do you personally think you have?

- Slight or low risk ☐
- Average risk ☐
- Above average risk ☐
- High or very high risk ☐
- Certain to get breast cancer ☐

4) Since you received your risk assessment how concerned have you been about your risk of breast cancer?

- Not at all ☐
- A little ☐
- Quite a bit ☐
- Very much ☐

5) What do you think the risk is of developing breast cancer for **any** woman in the general population in her life-time? (Please circle one)

a) inevitable
b) 1 chance in 2
c) 1 chance in 3
d) 1 chance in 4
e) 1 chance in 5
f) 1 chance in 6
g) 1 chance in 8
h) 1 chance in 10
i) 1 chance in 12
j) 1 chance in 20
k) 1 chance in 50
l) 1 chance in 100
m) very likely

6) On a scale from 0 (definitely will **not** get it) to 100 (definitely **will** get it), what do you think the risk of developing breast cancer for **any** woman in the general population in her lifetime? (Please circle)

0.....10.....20.....30.....40.....50.....60.....70.....80.....90.....100%

definitely will **not** get it — definitely **will** get it

7) What do you think your life-time risk is of developing breast cancer
(Please circle one)

a) inevitable
b) 1 chance in 2
c) 1 chance in 3
d) 1 chance in 4
e) 1 chance in 5
f) 1 chance in 6
g) 1 chance in 8
h) 1 chance in 10
i) 1 chance in 12
j) 1 chance in 20
k) 1 chance in 50
l) 1 chance in 100
m) very likely

8) On a scale from 0 (definitely will **not** get it) to 100 (definitely **will** get it), what do you think your lifetime risk is of developing breast cancer. (Please circle)

0.....10.....20.....30.....40.....50.....60.....70.....80.....90.....100%
definitely will **not** get it — definitely **will** get it

9) In your opinion would you say your chances of getting breast cancer are:

- Much higher than the average woman ☐
- A little higher than the average woman ☐
- Same as the average woman ☐
- Lower than the average woman ☐
- Much lower than the average woman ☐
- Unsure ☐

10) Since you received your risk assessment, have you discussed any concerns that you may have about breast cancer with your family of origin (ie the family you were brought up in: eg mother, father, sisters or brothers)?

- Rarely or not at all ☐
- Sometimes ☐
- Often ☐
- Most of the time ☐

11) Since you received your risk assessment, have you discussed any concerns about breast cancer with your husband/partner?

- Rarely or not at all ☐
- Sometimes ☐
- Often ☐
- Most of the time ☐

YOUR EXPERIENCES OF ASSESSMENT FOR GENETIC RISK OF BREAST CANCER

We would like to ask you a few more questions about your recent experiences of assessment for genetic risk of breast cancer. There are no right or wrong answers: we are interested in your real opinions and feelings, as this will help us to improve our Family History Breast Cancer service. Please read carefully each of the following questions and tick the statement which best describes your feelings.

1) Overall, how satisfied were you with the way your genetic risk assessment was handled? (Please tick one box)

- Very satisfied ☐
- Quite satisfied ☐
- A bit satisfied ☐
- Very dissatisfied ☐ (please describe)

2) How satisfied were you with the information you got?

- Very satisfied ☐
- Quite satisfied ☐
- A bit satisfied ☐
- Very dissatisfied ☐ (please describe)

_____

_____

_____

3) Were explanations clear in understandable, everyday language?

- Very satisfied ☐
- Quite satisfied ☐
- A bit satisfied ☐
- Very dissatisfied ☐ (please describe)

_____

_____

_____

4) Were you satisfied with the amount of information you received

- Yes, about the right amount ☐
- No, not enough information ☐
- No, too much information ☐
- Unsure ☐

5) Were any of your questions left unanswered? (Please tick one box)

Yes, a few ☐ Yes a lot ☐ No ☐

If Yes please give an example:_____

_____

_____

6) Did you want precise information about your risk of developing breast cancer?

Yes ☐ No ☐ Unsure ☐

7) Did you receive the right amount of information about your risk?

Yes, about the right amount ☐
No, not enough information ☐
No, too much information ☐
Unsure ☐

8) How did you feel about the way you were informed?

Very satisfied ☐
Quite satisfied ☐
Not sure ☐
A bit dissatisfied ☐
Very dissatisfied ☐

9) Was the level of risk you were given different from what you had expected?

Lower than expected ☐
Higher than expected ☐
About the same as expected ☐
I didn't know what to expect ☐
I wasn't told my risk ☐

10) How do you feel now that you have been told about your risk of developing breast cancer?

Please describe in a few words _____

_____

_____

11) Has the counselling that you received helped you to cope better with your problem?

- No, not all ☐
- A little ☐
- Quite a bit ☐
- Very much ☐

12) How satisfied were you with the length of time you waited between returning the family history questionnaire to us and receiving your risk assessment.

1.....2.....3.....4

very dissatisfied very satisfied

Appendix D

GP questionnaire

GP Questionnaire

Ref:

RE: «Prename» «Surname» («Date_of_birth» «MPI»)
«Address», «Area», «Town» «Postcode»

1. Were you satisfied with the information and service provided? YES / NO

If No, please indicate briefly the reason(s) ……
……

2. As far as you are aware, was your patient satisfied with the information/service provided?
YES / NO

If No, please indicate briefly the reason(s) ……
……

3. Since receiving her letter or interview, has the patient contacted you again to discuss breast cancer risk? YES / NO

If YES, please indicate briefly the reason(s) ……
……

4. How do you feel about a triage process whereby risk is fully assessed before a decision is taken whether or not to offer a patient a cancer genetics appointment?

Completely satisfied ☐
Some reservations ☐
Major reservations ☐
Strongly opposed ☐

5. Would you be willing to participate in focus group meeting to explore further issues relating to organisation of cancer genetics services? YES / NO

6. Please add any comments on NHS cancer genetics services – local or national.
……
……
……
……
……

Thank you for completing this questionnaire.

For office use only:

Please send payment of £10.00 To

«Clinician_Name» «Address_1» «Address_2» «Address_3» «Address_4»

Thank you
…….(signed)