ESTABLISHMENT AND EVALUATION OF A NEW CLINICAL SERVICE FOR WOMEN WITH A FAMILY HISTORY OF BREAST CANCER.
ABSTRACT

In 1992, a new clinical service for women with a family history was established in Edinburgh. This runs as a multidisciplinary clinic with surgeons, geneticists, breast screening radiologists, nurses and a psychologist. The service was one of the first of its kind to be set up in the UK.

The work included in this thesis relates to the first three years’ experience with this clinic.

Demand for the service is sustained and its provision is welcomed by women and general practitioners alike. There appears to be a deficit of women in social classes IV and V making use of the clinic, even when the differing incidence of breast cancer amongst the social classes is taken into account. As with most screening programmes, efforts may be required to reach women from the more deprived sectors of the population.

Comparison was made with other similar recently established clinics. In particular, it was found that no ideal set of referral criteria could be established which would reliably ensure the referral of women at true increased risk whilst allowing those not at increased risk to be reassured in general practice. Nonetheless, given referral guidelines, GPs were as good as secondary care sources at identifying those for whom referral was appropriate.

Psychological assessment was included to monitor any potential adverse effects of clinic attendance, improvement in knowledge of risk after genetic counselling and what steps women themselves are prepared to take in managing their increased risk of breast cancer. As in other reports, prior knowledge of risk was poor. Although this improved after counselling, a number of women persisted in either over- or under-
estimating their risk by a significant degree. Fortunately, there were no adverse effects on anxiety levels, with most women reporting that they found attending the clinic helpful and reassuring. Most adopted a positive approach to health care with 90% having performed breast self examination in the past. There was no evidence in this cohort that women with a family history behave any differently from age-matched women from the general population in terms of other breast cancer risk factors such as oral contraceptive use and child-bearing.

An extensive review of the accuracy of family history reporting was undertaken. This essentially showed that women have a good knowledge of the cancer site of prime importance but that other cancer sites may be less accurately recalled. In general, breast cancer cases tended to be over reported rather than under reported although the latter was marginally more evident in second degree relatives. Nevertheless, the inaccuracies identified did not alter the decision to screen in a significant number of individuals, although the numerical risk estimate may have been altered. Whilst time consuming and costly, the checking processes enabled the tracing of pathological material which has been invaluable in furthering knowledge about the histology and behaviour of familial breast cancers. Where major interventions such as prophylactic surgery are being considered, such checking should be mandatory.
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AIMS

Ponder (1994) sets out the purposes of a familial cancer clinic. These are:-
1. To confirm, interpret and extend family histories of cancer.
2. To advise the individual and the general practitioner about risks and possible action to be taken.
3. To advise about the possibility and appropriateness of DNA-based testing and to arrange it if agreed, and to supervise the giving of results.
4. To provide a resource for research, including the evaluation of the clinic itself, which is important for future funding of familial cancer services.

The work reported in this thesis relates mainly to aim 4. The author was closely involved in the inception of a clinic in Edinburgh for women with a family history of breast cancer, with the evolution of clinic practice in its early years and with its evaluation. This is an account of observations made during the operation of that clinic including the results of formal evaluation of clinic services.

Issues to be evaluated are:-
1. The scale of demand for clinic services together with the sources(s) of that demand, accuracy of the perceived need and the demography of those women attending.
2. The accuracy of women’s knowledge about their family history of cancer and the impact of any changes made to this information by the ensuing checking mechanisms on risk estimate including the implications not only for the clinical service but also for the potential for future genetic research.
3. The impact of the service provision on the women attending including the impact on the accuracy of their own knowledge of risk level and their anxiety levels related to mechanisms of coping with stress.
4. General practitioner satisfaction with the service provided.

An appraisal of future directions in familial breast cancer services will be made in the light of this audit of the present service, based on both personal experience and on developments in basic human genetics and the management of breast cancer.
INTRODUCTION.
THE BURDEN OF BREAST CANCER.

Breast cancer is the commonest malignancy in females. One woman in 12 in Scotland can be expected to be affected with the disease by the age of 74. This is equivalent to an 8.5% lifetime risk of the disease. During the 1980s, breast cancer accounted for 24% of all malignant neoplasms in Scottish women; that is, on average 2600 new cases per year, resulting in 1250 breast cancer deaths per year (Sharp et al., 1993).

The age specific incidence of breast cancer shows a plateau at ages 45-50 which represents the division between pre- and post-menopausal cases (Figure 1). Very few cases occur under the age of 25. In the decade to 1990, 3252 cases of breast cancer occurred in Scottish women under 45 years of age. This represents 8.1% of the total. Over half of these were in the 40-44 years age group with only 129 cases occurring under the age of 30 (Sharp et al., 1993).

The annual incidence of breast cancer in Scotland is around 100 per 100,000 population, all ages taken together. The risk of breast cancer has long been known to be associated with socio-economic status. This holds true for the most recent Scottish data available, which exhibit a strong trend of increasing incidence with increasing affluence. The difference in incidence between the most affluent areas and the most deprived was almost 30% (Figure 2).

The cost of the treatment of breast cancer is dependent on the age at diagnosis and the stage of disease. Because treatment is largely tailored to the individual patient, dependent on these and other variables, the cost can be very difficult to estimate. However, most premenopausal patients receive adjuvant CMF chemotherapy (approximately 80% in the Edinburgh Breast Unit; M. Dixon, personal
communication). The cost of this regime has been calculated at £216 per patient per year of disease-free survival gained (Miles et al., 1990). This is in addition to the "one-off" costs of the initial surgery and radiotherapy. Nevertheless, these figures have to be set against estimated costs of treating benign disease such as ischaemic heart disease which have at least a comparable if not greater impact than cancer on the health of the nation. For example, procedures such as coronary artery bypass grafting may cost between £5,000 and £20,000 per year of life gained (Miles et al., 1990).

The introduction of newer, and perhaps more effective, chemotherapy regimes alters the balance of the cost-benefit equation as such drugs are more expensive. Substantial gains in survival, even in patients with metastatic disease, are now possible with chemotherapy regimens using the taxanes and monoclonal antibodies against the HER2 receptor. Monoclonal antibody technology, in particular, is extremely expensive and likely to remain so for the foreseeable future.

Much more difficult to estimate are the "hidden" costs of cancer treatment to the patient and her family, for example, in terms of time lost from gainful employment and cost of additional childcare facilities. While these may not pose so great a burden for the majority of breast cancer patients who are postmenopausal and perhaps already retired, to the young woman with breast cancer they are very real considerations. In these circumstances, prevention must always be considered better than cure. As primary prevention is not a real option in breast cancer for the immediate future it behoves the medical profession to investigate better means of early detection and possible cure for this disease.
AGE -SPECIFIC BREAST CANCER RATES IN SCOTLAND 1981-1990

FIGURE 1. from Sharp et al., 1993.
AGE STANDARDISED CANCER REGISTRATIONS BY DEPRIVATION CATEGORY

FIGURE 2.
FAMILIAL PREDISPOSITION TO BREAST CANCER.

The Ancient Romans are said to have recognised familial clustering of breast cancer cases as early as A.D.100 but formal documentation of family history as a risk factor did not begin until the mid-nineteenth century. The French physician Paul Broca (1886) described a family (thought to be his wife's) in which there were 10 deaths from breast cancer among 24 women, extending over 4 generations (Figure 3). The cases were mainly of early onset. He also recognised that aggregation of cancers in families could equally well be due to shared environmental factors as to an inherited predisposition to cancer.

Inherited predisposition to cancer in humans has now been accepted in medical texts as a real and important phenomenon for the past 40 years or so (Macklin, 1959). Epidemiological surveys have confirmed an increased risk of cancer in the relatives of breast cancer patients. The Nurses' Health Study in the USA recruited 117,988 women aged 30-55 years in 1976 and has followed them up ever since. Colditz et al. (1993) identified 2,389 incident cases of breast cancer from this cohort and calculated relative risks for those with and without a family history of the disease. A consistently elevated risk was found for those with an affected mother or sister, regardless of age at diagnosis. Overall, only 2.5% of breast cancer in this population could be attributed to family history. This is almost certainly an underestimate as inheritance of risk was considered only through the maternal lineage.

The Cancer and Steroid Hormone (CASH) study was a large population-based case-control study indicating an increased risk for the mothers and sisters of breast cancer cases dependent on age at diagnosis of the affected relative (Claus et al., 1991).
As previously alluded to, an increased risk of breast cancer within families could be due either to shared environmental factors or to genetic predisposition or both. Several studies have been carried out to confirm a genetic component and to elicit the mode of inheritance of breast cancer predisposition, employing the method of complex segregation analysis. Pedigrees ascertained from breast cancer patients are subjected to mathematical modelling to test the goodness of fit of the observed breast cancer cases to various modes of inheritance under Mendelian laws. Thus the probability of autosomal dominant, recessive and polygenic inheritance can be calculated. A maximum likelihood score is obtained which may favour one model so strongly as to virtually eliminate the others (Steel et al., 1991). Segregation analyses of this type undertaken in breast cancer kindreds from various European countries and the USA are in agreement that the most likely mode of inheritance is a single locus autosomal dominant gene with a high degree of penetrance. Williams and Anderson (1984) conducted segregation analysis on 200 breast cancer pedigrees of Danish extraction. Proband were identified through the population based resource of the Danish Cancer Registry. Thus this particular study is not subject to the same criticism as some others where pedigrees for analysis have been selected on the basis of a strong family history, introducing potential bias into the calculations. First and second degree relatives were taken into account. All reports of cancers were verified by reference to death certificates, hospital records and cancer registration data. In all, 95% of the reported cancers could be confirmed by at least one of these means. The results implied that a major locus alone was sufficient to account for the observed distribution of breast cancer in these pedigrees. A dominant model explained the segregation pattern much better than a recessive model.
Additional tests were carried out to detect departure from a Mendelian mode of inheritance, a hypothesis which was rejected. Estimates of heritability provided support for the assumption that breast cancer susceptibility is transmitted equally through paternal and maternal lines. This confirmed the work of several other groups reported previously (Macklin, 1959; Anderson, 1974; Tulinius et al., 1982).

Penetrance of the abnormal allele increases with age. A female heterozygote in this data set has a 57% chance of developing breast cancer by age 80. Conversely, the frequency with which affection can be attributed to the abnormal allele decreases with age. In other words, the proportion of sporadic cases (phenocopies) is greater in the older age groups. The authors calculate that prior to the age of 30 years, 88% of affected females within multi-case families are heterozygous carriers, whereas by the age of 80 this proportion has decreased to 13%. These results agree with the evidence from epidemiological studies demonstrating a greater increase in risk of breast cancer amongst relatives of premenopausal patients than in relatives of postmenopausal patients.

Other segregation analyses have been performed but, as mentioned above, all have been subject to ascertainment bias in that families were selected for inclusion on the basis of a strong family history of breast cancer. Nevertheless, broadly similar results to those of the Danish study were obtained by most investigators. Go et al. (1983) conducted segregation analysis of 18 families registered with the Creighton University breast cancer family resource. Again, the best overall explanation for the observed pattern of breast cancer cases was an autosomal dominant mode of inheritance. All modes of inheritance were significantly more likely than an environmental model alone in all except two families.
Families in this study were also pooled according to certain tumour associations postulated by Lynch et al. (1971; 1973). For families segregating both breast and ovarian cancer there was no loss of fit to an autosomal dominant model, but the environmental hypothesis fitted significantly less well. Inclusion of cancers at sites other than breast or ovary as part of the gene expression, however, led to rejection of the genetic hypothesis. An association between breast and gastrointestinal cancers was better explained by an environmental hypothesis than by a genetic one. However, since this category included only two families this conclusion must be regarded with extreme caution. Breast and endometrial cancers were postulated to be genetically associated although no one mode of inheritance was significantly more likely than any of the others. Two families exhibited cancer inheritance patterns compatible with Li-Fraumeni syndrome (p. 28).

Due to the small sample size and the recognised ascertainment bias in this study, it is impossible to distinguish conclusively between the different modes of inheritance or to estimate with any degree of accuracy the gene frequency and penetrance. In addition, since it was impossible to define the population from which the sample families were drawn, no estimate of the proportion of breast cancer in the general population that may be genetically influenced could or should be made. Age-specific penetrances calculated from these data are almost certainly an over-estimate both because of the selection bias and because no allowance was made for the possibility of sporadic cases occurring within genetically predisposed families.

Iselius et al. (1991) carried out segregation analysis on a number of British families and it is therefore to be expected that the results from their study might be more directly applicable to counselling of women in this country. Two samples were
collected: a consecutive series of women undergoing treatment for histologically proven breast cancer and a second series of women attending a genetic counselling clinic who were, by definition, selected on the basis of having a positive family history of the disease. Both groups were analysed together in the segregation analysis. The results again agree with previous studies in that a dominant major gene is strongly favoured as the best fit to the observed pattern of inheritance. The gene frequency was estimated at 0.003 with a lifetime penetrance of 0.83. Inherent in this model is the fact that an individual with breast cancer in a low-risk group (e.g. young age) is more likely to carry the putative breast cancer gene than an affected individual belonging to a higher risk group (e.g. older age group). That is, “liability-class” is age dependent. The probability of being a gene carrier when affected at a given age together with age-specific penetrances taken from these data are given in Table 1.

Both endometrial and ovarian cancers were significantly associated with breast cancer in this study. There was also an over-representation of cancers at other sites such as sarcomas, embryonal malignancies, acute leukaemias, thyroid tumours and Hodgkin's disease. This is in keeping with reports elsewhere (Lynch and Krush, 1971; Li and Fraumeni, 1969). An attempt was also made to analyze the proportion of bilateral cases in familial versus sporadic breast cancers and a significant excess found among the former. However, the authors stipulate that these figures should be viewed with caution as, in many instances, laterality was unknown, the only information available being that a given individual was affected.
<table>
<thead>
<tr>
<th>Age of onset</th>
<th>Probability of being gene carrier</th>
<th>Penetrance</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-24</td>
<td>0.897</td>
<td>0.007</td>
</tr>
<tr>
<td>25-29</td>
<td>0.833</td>
<td>0.020</td>
</tr>
<tr>
<td>30-39</td>
<td>0.405</td>
<td>0.171</td>
</tr>
<tr>
<td>40-49</td>
<td>0.202</td>
<td>0.387</td>
</tr>
<tr>
<td>50-59</td>
<td>0.138</td>
<td>0.541</td>
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<tr>
<td>60-69</td>
<td>0.109</td>
<td>0.656</td>
</tr>
<tr>
<td>70-79</td>
<td>0.097</td>
<td>0.735</td>
</tr>
<tr>
<td>80+</td>
<td>0.076</td>
<td>0.829</td>
</tr>
</tbody>
</table>

**TABLE 1.**

From Iselius et al., 1991.
Further elucidation of the inheritance of breast cancer requires the technique of genetic linkage analysis in which the co-inheritance of specific DNA markers and the disease is tested. The closer any given marker is situated to the putative breast cancer gene, the less likely it is that any recombination will occur between them and therefore the more likely that they will be inherited together i.e. that they are linked. This enables calculation of a lod score (log of the odds of linkage). That is, the log of the ratio of the likelihood of finding this (or a more extreme) distribution of the disease and the marker if they are linked with θ recombination rate versus the likelihood of finding this distribution if they are unlinked. A lod of +3 thus indicates a likelihood ratio in favour of linkage of 1000:1 and is taken as good evidence of the presence of a breast cancer predisposing gene in that region. Negative lods of 2 or more are considered conclusive evidence against linkage to that particular marker. The results of many studies employing this method will be discussed in the next section.

GENETICS OF BREAST CANCER.

As explained in the previous section, familial breast cancer on the whole exhibits an autosomal dominant pattern of inheritance. This is consistent with the existence of one or more tumour suppressor genes. These are a family of genes present within all normal cells which exert a negative control over cell growth and replication. Mutation in a tumour suppressor gene causes loss of function and results in disordered cell growth. The prime example of how tumour suppressor genes are implicated in hereditary cancers comes from Knudson's work on retinoblastoma (1971). According to Knudson's hypothesis an individual who inherits a mutation in one copy of a
tumour suppressor gene is at increased susceptibility of developing cancer which occurs following a further mutation in the remaining normal copy of the gene. The first mutation is termed germline and the second sporadic; the overall theory is the two-hit hypothesis. The same theory can be used to explain sporadic cancers but here two somatic events are required for the development of cancer; thus hereditary cancers tend to have an earlier age of onset than sporadic cases of the same disease. Also, individuals who already carry one mutation are liable to have multiple primary tumours. The causative mutations are recessive at the cellular level but the cancers exhibit a dominant pattern of inheritance.

BRCA1

Linkage analysis has enabled the location of several breast cancer susceptibility genes. The first, designated BRCA1, is situated on the long arm of chromosome 17 (17q). This gene appears to play an important role in families where the age of onset of breast cancer is <45 years or where both breast and ovarian cancer occur in the same family (Hall et al., 1990; 1992). Another study of 31 breast cancer families and 12 breast-ovarian cancer families showed clear evidence of linkage to BRCA1 in families with ovarian cancer, but only weak evidence in those without ovarian cancer (Smith et al., 1993). The authors suggest that these results provide further support for the theory that other genes contribute significantly to breast cancer susceptibility. Not only does BRCA1 predispose to both early onset breast cancer and ovarian cancer, but there is now good evidence for an increased susceptibility to prostate and colon cancers. Male carriers of BRCA1 mutations are at increased risk of prostate carcinoma while carriers of both sexes have a greater risk than the general population.
of developing colon cancer (Ford et al., 1994). More recent data from the same researchers also suggest an increased risk of pancreatic, endometrial and cervical cancers. However, the additional risk of cancers other than those of the breast or ovary, is probably very small (Thompson et al., 2002).

BRCA1 was finally cloned in 1994 (Miki et al.). Preliminary work on mutational analysis of this gene confirms that in most aspects it fits the hypothesis of being a tumour suppressor gene. Probable predisposing mutations were detected in five out of eight families presumed to be linked to BRCA1. In two of the kindreds in which no mutation was found the lod scores were -0.20 and -0.44, indicating that the original assumption of linkage in these families may in fact have been erroneous.

In BRCA1 mutation carriers affected by either breast or ovarian cancer the wild-type allele was invariably lost from the tumour cells while the mutant copy was retained (Merajver et al., 1995). Loss of heterozygosity (LOH) studies have shown losses (and down regulation) in the BRCA1 region in 30 to 70% of sporadic breast and ovarian carcinomas (Eccles et al., 1990; Cropp et al., 1994). The observation of potential predisposing mutations in individuals with early-onset breast cancer who were not ascertained on the grounds of a family history of the disease lends further support to the theory that BRCA1 is a tumour suppressor gene with an important role in early-onset cases (Futreal et al., 1994). However, on closer inspection, these mutations were present in the germline rather than being somatic mutations. This absence of somatic mutations in BRCA1 was unexpected given the frequency of LOH in this region and the large size of the gene. This led Futreal to postulate that BRCA1 mutations may only have an effect on tumour development when present at a specific stage such as during puberty when the breast and ovarian tissues are particularly sensitive to
hormonal stimulation. BRCA1 is large in genetic terms, being some 100,000 base pairs in size and containing 23 exons. The largest exon is number 11 which accounts for around 60% of the coding sequence. The full-length protein product consists of 1,863 amino acids with a zinc finger RING motif at the N terminus. Apart from this it bears no homology to any other known gene product. The zinc finger is a DNA binding domain which suggests that BRCA1 may function as a transcription factor regulating gene expression (Wu et al., 1996).

The nature of several mutations observed in BRCA1 is consistent with either dominant-negative proteins or non-functional proteins, a mechanism which has already been established in the case of other tumour suppressor genes such as p53 (Lane, 1992), WT1 (Little, 1993) and some alleles of APC (Su et al., 1993). To date a huge spectrum of mutations has been identified and most appear to be true mutations rather than polymorphisms (Table 2). Over 70% of these mutations result in the loss or premature termination of protein synthesis. Given the genetic heterogeneity of hereditary breast cancer, the heterogeneity of mutations within BRCA1 itself and the large size of the gene, mutation screening will be technically challenging (Castilla et al., 1994).
<table>
<thead>
<tr>
<th>MUTATION</th>
<th>CUMULATIVE FREQUENCY</th>
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<tr>
<td>185del AG</td>
<td>11%</td>
</tr>
<tr>
<td>5382insC</td>
<td>19%</td>
</tr>
<tr>
<td>1294del40</td>
<td>25%</td>
</tr>
<tr>
<td>Cys61Gly</td>
<td>29%</td>
</tr>
<tr>
<td>4184del4</td>
<td>34%</td>
</tr>
<tr>
<td>Arg1443ter</td>
<td>37%</td>
</tr>
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</table>

**TABLE 2.**
Cumulative frequency of BRCA1 mutations

BRCA2

Not all families with hereditary breast cancer are linked to BRCA1. In fact, only up to an estimated 50% are linked (Stratton, 1996; Table 3). This implies that there are other tumour suppressor genes involved in familial cases of the disease. Evidence for one such gene came initially from studies of families containing at least one case of breast cancer in a male member (Stratton et al., 1994). Linkage analysis in these families pointed to a locus on chromosome 13q close to but separate from and distal to the retinoblastoma gene (Wooster et al., 1994). This has been designated BRCA2 and, in most populations studied to date, may account for up to 30% of familial breast cancers (50% if only site-specific breast cancer is considered). BRCA2 confers a similar risk to BRCA1 of breast cancer to female carriers. The risk of ovarian cancer is much lower but the risk of breast cancer in male carriers is markedly greater (around 5%; Stratton, 1996). An excess of prostate, skin melanoma, pancreatic, oral, laryngeal and cancers of the biliary tree has been demonstrated in BRCA2 linked families (Breast Cancer Linkage Consortium, 1999).

BRCA2 has now also been cloned (Wooster et al., 1995). Like BRCA1 it is a large gene with a 10-12 kilobase transcript encoding a 2,329 amino acid product. There is no strong homology with known DNA or protein sequences and thus no clues are as yet available as to its function. Preliminary investigations suggest that it does indeed meet the criteria for a tumour suppressor gene and that it may be involved in the regulation of excessive cell multiplication.

Both BRCA1 and BRCA2 seem to associate with RAD51 which is implicated in homologous chromatid interchange in repair of DNA damage. Hence they may be "caretaker" genes (Kinzler and Vogelstein, 1997).
BRCAx

Clearly there is a significant proportion of families unlinked to either BRCA1 or 2 and for which one or more tumour suppressor genes remain as yet to be identified. For the time being these are attributed to “BRCAx.” They seem to have distinct pathological features when compared to BRCA1 and BRCA2 cancers, such as lower nuclear grade, fewer mitoses and more tubule formation, all of which confer a better prognosis (Lakhani, et al., 2000). Postulated loci include chromosomes 7q (Bieche et al., 1992;), 8p (Kerangueven et al., 1995), 6q (Devilee et al., 1991) and 16q (Dorion-Bonnet et al., 1995).

RER Genes

The Lynch type II hereditary cancer syndrome consists of non-polyposis colon cancer in young adults together with pelvic (chiefly uterine and ovarian), urothelial, gastric and skin malignancies. Some families also have individuals with sarcomas and brain tumours and in one study a relative risk for breast cancer of 5 has been reported (Itoh et al., 1990). Recent studies have identified at least four separate genes associated with this syndrome. All are involved in DNA mismatch repair. They are hMSH2 on chromosome 2p (Fishel, 1993); hMLH1 on chromosome 3p (Papadopoulos et al., 1994); and hPMS1 and hPMS2 on chromosomes 2q and 7q respectively (Nicolaides et al., 1994). As yet the absolute risk of breast cancer in carriers of these mutations has not been calculated, but it appears to be low. Again, there is some evidence for increased ovarian cancer risk also.
<table>
<thead>
<tr>
<th>GENE</th>
<th>LOCATION</th>
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<th>PERCENTAGE OF ALL BREAST CANCER UNDER 50 YEARS</th>
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<tbody>
<tr>
<td>BRCA1</td>
<td>17q</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>A-T</td>
<td>11q</td>
<td>?</td>
<td>7</td>
</tr>
<tr>
<td>p53</td>
<td>17p</td>
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<td>&lt;1</td>
</tr>
<tr>
<td>BRCA2</td>
<td>13q</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Lynch type I</td>
<td>2p, 3p</td>
<td>?5</td>
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**TABLE 3.**
p53

p53 is a tumour suppressor gene located on chromosome 17p. Somatic mutations in this gene have been described in up to one third of all breast tumours (Coles et al., 1992; Thompson et al., 1992). Although germline mutations in p53 play only a limited role in hereditary breast cancer in terms of the number of cases attributed to this gene, it deserves particular mention here because of its importance in the rare cancer family syndrome known as Li-Fraumeni syndrome (Li and Fraumeni, 1969; Malkin et al., 1990). In this syndrome soft tissue sarcomas and childhood cancers (particularly of embryonal tissues) are associated with early-onset breast cancer.

Cowden’s Disease

Cowden’s disease is an autosomal dominant cancer predisposition syndrome associated with an elevated risk for tumours of the breast, thyroid, bowel and skin (Lloyd and Dennis, 1963). The gene for this disease has been localized to chromosome 10q (Nelen et al., 1996). Mutations of the tumour suppressor gene PTEN which lies in this region have subsequently been identified in 4 out of 5 families with this syndrome (Liaw et al., 1997).

Ataxia-Telangiectasia.

This is again a rare syndrome and the importance of the AT gene in familial breast cancer is controversial. It is inherited as an autosomal recessive condition. Swift et al. (1987) described a one-hundred fold increased incidence of leukaemias and lymphomas in AT patients. In addition, AT heterozygotes show a striking predisposition to cancer and excessive sensitivity to ionising radiation, a factor which
may be important in the development of sporadic breast cancers and which may make screening for breast cancer in these families by mammography inadvisable. The relative risk for breast cancer in female AT heterozygotes may be as high as 6.8 (Swift et al., 1990) although other reports have failed to confirm this (see below). Mutations in the AT gene primarily predispose to breast cancer at all ages and may be responsible for 9 to 18% of all breast cancer in the population as a whole. Some authors have also postulated that only certain AT mutations carry an increased risk for breast cancer (Nevanlinna, unpublished data). The AT gene is located on chromosome 11q 22-23 and has now been cloned (Savitsky et al., 1995). The gene encodes a 3056 amino acid protein product which appears to play a role in maintaining genome stability. Most mutations so far identified lead to truncation of the protein (Bishop and Hopper 1997; Fitzgerald et al., 1997; Stankovicz et al., 1998). Bishop and Hopper (1997) found no direct evidence for an excess of AT mutations in breast cancer cases, nor of an increase in breast cancer amongst AT heterozygotes. However, the data were inconclusive and a genuine causal association was not formally ruled out.

DETECTION OF GENETIC MUTATIONS
Where a specific gene has not yet been cloned, the only method of determining putative gene carriage is by genetic linkage analysis. This technique relies on the availability of polymorphic markers situated close to the gene under investigation (linked markers) and a sufficient number of samples from affected family members. Even given that both of these conditions are fulfilled there is still an appreciable degree of uncertainty with the results.
Direct testing for mutations proven to predispose to the disease offers the best hope for familial breast cancer patients. This may be accomplished by one or more of a number of methods, each with its own short-comings (Connor and Ferguson-Smith, 1993).

Allele Specific Oligonucleotides (ASO).

This technique employs short probes (17-30 nucleotides) with sequences complementary to either normal DNA or mutant DNA at the region of interest. Under appropriate experimental conditions, the presence or absence of hybridisation with these probes will distinguish normals from heterozygotes or homozygous affected individuals.

Heteroduplex Scanning.

Single strand normal and mutant DNA are amplified by the polymerase chain reaction (PCR) and hybridised to form heteroduplexes. Areas of mismatch in the DNA sequence occurring at the site of mutations are detected by altered electrophoretic mobility in special gels or can also be identified by susceptibility to chemical cleavage.

Single Strand Conformation Polymorphisms (SSCP).

The mobility of PCR amplified DNA in electrophoretic gels depends on both its size and sequence. Even some single base changes may be detected as mobility shifts. However, sensitivity of the technique depends on the precise nature of the base change and its position within the amplified fragment. SSCP also detects non-
pathogenic variants (polymorphisms) which are relatively common in BRCA1 and BRCA2.

Direct Sequencing.
This method has always been very time consuming although with the advent of PCR amplification of target sequences and the introduction of automated processors its routine use is becoming more practical. It can be used to confirm point or other small mutations identified by any of the above methods.

Protein Truncation Test (PTT).
This method depends on the fact that many of the mutations of interest cause premature cessation of transcription or translation, resulting in a protein product that is shorter than normal. This truncated protein is then detected by gel electrophoresis. It is relatively quick and simple to perform, its main drawback lying in the fact that not all mutations are protein-truncating. However, as around 75% of the common BRCA1 mutations are in fact protein truncating, there is real potential for the use of this technique in mutation screening (Shattuck-Eidens et al., 1995). So far detection rates by PTT have been disappointingly low, at around 20% of “high risk” families screened (Hogervorst et al., 1995).

DNA Microchip Technology.
This approach is a combination of light-directed synthetic methods employed in the semi-conductor industry and standard oligonucleotide synthetic chemistry. A series of microchips can be prepared in a relatively short space of time, containing potentially
hundreds of thousands of oligonucleotides of predetermined sequence which are designed to interrogate a DNA or RNA sample for sequence or expression information.

The technique has already been applied to exon 11 of BRCA1 and can successfully detect substitutions as well as small insertions and deletions (Hacia et al., 1996). It is, however, expensive to set up, and technically demanding both in performance and analysis.

RISK ASSESSMENT

Determining the probability that a given individual will develop breast cancer is often very difficult. The overall risk is determined by a combination of genetic factors and environmental influences; the latter including such internal environmental factors as hormone levels. For the few women who are strongly genetically predisposed to the disease the genetic factors predominate whilst for the majority of the population it is the environmental factors which are most important. Whilst environmental factors such as early age at menarche, parity and late age at menopause are well documented, their importance in any individual’s case is currently impossible to determine. Most models for assessing risk have therefore tended to assume that the environmental factors are more or less constant for everyone and take into account only the genetic component. What is therefore being assessed is in fact risk relative to a woman of similar age and reproductive history, without the additional genetic component. Gail et al. (1989) derived a model whereby the interaction of genetic and environmental risk factors could be taken into account. However, this was validated on screened patients over the age of 50 years and may not therefore be directly applicable to the
younger population in which the genetic component is relatively more important. A further attempt to validate the model in women with a positive family history concluded that it predicted the risk well for those who adhered to the recommendation of the American Cancer Society that they should be in receipt of annual mammograms. The model was less accurate in those who did not fulfil this criterion in that it overpredicted risk for women younger than 60 years and tended to underpredict for women aged 60 years and older (Bondy et al., 1994).

Many of the known risk factors for breast cancer are outwith the control of the individual e.g. early age at menarche. By the time she presents to the familial breast cancer clinic the opportunity to alter others such as number of pregnancies and age at the first one may have passed. What women are therefore primarily interested in is their residual genetic risk and ways in which this can either be avoided or modified.

Many methods of presenting risk to patients have been tried, all of which have their drawbacks. One way is to give a figure for total lifetime risk but this has very different implications in practice for individual women. For example, the actual risk of breast cancer will be lower for a woman of 70 than for a woman of 40 with the same lifetime risk, as the former has already lived through most of her risk without developing the disease. What actually matters is her risk of developing breast cancer during the remainder of her lifetime which can be presented as residual risk. In order to plan for the future, some women may wish to know their chances of being affected within, say, the next ten years.

Numerical risk data seem to have little meaning for many women. Evans et al. (1993) found that only 11% of women could correctly identify the general population risk. Despite believing their own risk to be increased, they could not distinguish between
this and that of the general population. It may therefore be more relevant to present risk in a non-numerical format such as slightly increased, moderately increased or greatly increased with respect to that of the general population.

BREAST SCREENING

There are several prerequisite conditions underlying any screening programme. These are:

(i) that the disease can be detected at an early stage,

(ii) that an effective treatment is available and

(iii) that early treatment carries a better prognosis than treatment at a later stage.

The disease must also occur with sufficient frequency to make screening cost effective. Thus an effective screening modality must be available and the natural history of the disease must be sufficiently prolonged to allow earlier intervention to be effective.

The screening method used should be both highly sensitive and highly specific. That is, it should pick up a high percentage of cancers without picking up a large number of non-cancerous abnormalities. In this way, few cancers are missed while keeping the number of benign biopsies (as the result of a false positive screening examination) to a minimum.

The positive predictive value of a test is dependent on the prevalence of the disease. As prevalence decreases this dependence increases. Thus in younger women in whom breast cancer is less common, the positive predictive value of mammography is likely to be lower. In other words, a higher proportion of those screened will undergo further investigation for abnormalities which turn out to be benign.
The introduction of a successful screening programme for breast cancer is therefore dependent on:

1. Prevalence of breast cancer in the population
2. Identification of a sub-group at increased risk for breast cancer
3. Availability of an effective screening modality (in this case mammography). Any such screening test must be acceptable to the target population as must further investigation of any abnormalities detected.
4. Availability of effective treatment for the disease.

In 1988 the UK National Breast Screening Programme was set up, based on the evidence from several trials of breast screening (Forrest Report 1990). The programme allows for three-yearly single oblique mammography in women aged 50-64. Women over this age are not presently invited for screening due to poor compliance in this age group in the trials, but they are allowed free access to screening on their own initiative. As more women now live longer, the programme is to be extended up to the age of 70 in the near future.

The decision to begin screening at 50 years was based on the lack of evidence of a significant benefit in younger women. None of the randomised controlled trials (HIP, Malmo, Swedish two counties; Shapiro et al., 1971, Andersson et al., 1988, Tabar et al., 1989) showed a significant reduction in mortality in this age group. It was assumed that this was due to two factors:-

1) Relative lack of sensitivity of mammography in younger women with denser breast tissue

and

2) Too long an interval between screens.
More recent long-term follow-up data from both the HIP New York and the Swedish two counties trials have demonstrated a possible benefit from screening in women aged 40-49. (Tabar 1993, Dupont 1994). Although a consistent reduction in mortality can be shown, this fails to reach statistical significance. A controlled randomised trial of screening in this age group is under way in the UK but it will be several years before conclusive results are available.

The decision to recommend single oblique medio-lateral mammography alone has been criticised by some radiologists. However, the "miss" rate from this mode of screening has been estimated at less than 5% (Andersson et al., 1978). Similarly, mammography alone was not significantly less effective at detecting cancers (in terms of both sensitivity and specificity) than mammography together with clinical examination (Table 4). However, these findings may not be directly applicable to younger women in whom the breast tissue exhibits a more radio-dense pattern.

Specificity is an important consideration in any screening programme but arguably more so in one designed for young women at risk of breast cancer. In the United States, between 3 and 7 benign breast biopsies were generated for every cancer detected by mammography in the 40-49 age group. Excess biopsies are commoner in younger age groups (Baker, 1982). Whilst a relatively simple procedure, excision biopsy is not without morbidity and adverse cosmetic effects, particularly if multiple biopsies are carried out from the same breast. A balance must be struck between years of life saved and anxiety induced plus other risks from screening.

The optimal interval between screens can be determined by mathematical modelling and cost-benefit analysis. These figures can only be verified by carefully conducted trials of different screening intervals. The interval cancer rate i.e. those cancers
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<th>Sensitivity(%)</th>
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<td>1st round</td>
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<tr>
<td>Clinical only</td>
<td>47</td>
<td>62(50-78)</td>
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<td>Clinical+ mammography</td>
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<td>Mammography alone</td>
<td>86(78-94)</td>
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**TABLE 4.**
Reproduced from Forrest Report page 57.
presenting clinically following a negative mammographic screen, is an indication of the efficiency of screening. The UK National Breast Screening Programme screening interval is currently three years but recent data (Woodman et al., 1995) have shown that this is almost certainly too long and negotiations are under way to reduce it to two years, as favoured by the results of the Swedish two counties trial (Tabar et al., 1987). In younger women, even this interval may result in an unacceptably high interval cancer rate due to the presence of a population of particularly fast-growing tumours. Tabar et al. (1993) therefore recommend annual mammography in women aged 40-49.

It has been argued that the sensitivity of mammography is low in pre-menopausal women due to the radiodensity of the glandular breast tissue. Most studies do not seem to confirm this impression. In the Swedish two counties trial only 26% of the screened population in the 40-49 age group had a dense breast parenchymal pattern (Tabar and Dean, 1982). Meyer et al. (1983) showed that 28 out of 31 breast cancers diagnosed in women under 35 were mammographically visible and that microcalcification associated with carcinoma is rarely obscured by dense breast parenchyma. However, these results were obtained from patients attending a symptomatic breast clinic, most of whom had palpable abnormalities, and may not therefore be directly applicable to the screening situation.

A more extensive study by Bassett et al. (1991) in which they determined the indications for mammography in 1,016 women aged under 35 attending a symptomatic breast clinic concluded that "in no woman less than 35 years of age did mammography reveal a cancer without associated clinical signs or symptoms." This study included a small number of women who underwent mammography because of a
family history of breast cancer in a mother and/or sister. No cancers were detected in this subset. Negative mammographic findings contributed to a delay in biopsy in three patients with cancer. The authors recommend that mammography in the under 35s should be confined to those with sufficient clinical indication.

Amongst the factors determining the success of a screening programme mentioned earlier (p. 35), was the identification of a group of patients at increased risk for the disease. One such group is women with a family history of breast cancer. It may be that their risk is sufficiently high and the disease sufficiently prevalent amongst this group to allow them to benefit from screening where women of a similar age from the general population do not. A trial to test this hypothesis has been proposed (Howard Cuckle, personal communication) but has not yet begun. It is envisaged that such women would not be prepared to accept randomisation to screening or non-screening arms and it is therefore proposed to use the control population of the 40-49 trial already in progress as a control group for this trial also.

A major concern in offering screening by mammography to young women is the potential risk of radiation induced cancers. Most of the evidence for radiation risk is historical and comes from the follow-up of women exposed to high doses of ionising radiation as the result of nuclear warfare or radiotherapy treatment of benign conditions (Feig, 1984). Calculations based on these data may not therefore be applicable to mammography where the radiation doses are relatively small and where repeat exposures are spaced out over an extended time period.

The following general conclusions can be drawn from these studies:-

1. There is a minimum latent period of ten years between exposure and radiation induced cancer
2. Younger women exhibit a longer latent period as radiogenic breast cancers present clinically at the same ages as other breast cancers.

3. The increased risk persists for the rest of the patient's life.

4. Risk is dependent on age at exposure.

Law (1997) has calculated that, for women aged 30 and over with a family history of breast cancer, cancer induction rates would not exceed 120 per million, assuming a one year screening interval, provided guidelines for mean glandular dose of radiation are followed.

PSYCHOLOGICAL IMPACT.

Women with a family history of breast cancer have been repeatedly shown to be profoundly affected by this experience. The actual effects on the individual seem to depend on the closeness of the family relationship and the age of the woman when her relative was first diagnosed.

Kelly (1980) interviewed 39 women with a maternal history of breast cancer. Although the study numbers were very small, certain general conclusions can be drawn. Women who were adults at the time of their mother's diagnosis tended to be more shocked in the immediate days following hearing of this and to worry more about their own risk of breast cancer than those who were teenagers. Most women expressed feelings of guilt. Those who were teenagers felt guilty for failing to recognise the seriousness of their mother's illness. Adult daughters felt guilty because of ambivalent feelings of wanting to be with and help their mother but being so upset by her suffering that they often stayed away.

Most (82%) of the subjects perceived that their own risk of developing breast cancer
was increased because of their family history. 37 of the 39 women studied expressed anxiety about this risk and described several mechanisms of coping with this. 62% preferred not to think about it most of the time. 54% had sought medical reassurance at some stage. 79% performed breast self examination on a regular basis but both those who examined their breasts and those who did not were concerned that they would not be able to identify a malignancy should it arise in their own breast.

Although 92% of respondents in the above study thought that heredity could cause breast cancer, understanding of the magnitude of the genetic risk was very vague. Evans et al. (1993) in a pilot study of 155 women attending a familial breast cancer clinic found that only 11% could accurately assess the risk of breast cancer in the general population. 30% underestimated it by a factor of two and 24% overestimated by a similar amount. 26% were unable to distinguish their own risk from that of the general population in spite of thinking it increased. A later study from the same group (Evans et al., 1994) with larger numbers showed similar results but also assessed the impact of genetic counselling on the women's perception of risk. One year after risk counselling, subjects had a significantly better idea of their own risk and that in the general population. Retention of this knowledge was improved by sending women a letter outlining the main points of the clinic discussion. An important group of women was identified who persist in underestimating the risk both to the general population and to themselves, but who will attend for screening. This may well represent denial being used as a coping mechanism. Those women given risks which were lower than their own prior estimates appeared to benefit from the counselling process. Major concern remains over those who initially underestimate their risk and who may therefore be made more anxious by becoming better informed.
Similar results were found in a study of women volunteering for a familial ovarian cancer register (Green et al., 1993). While women had some perception of an increased risk they had little idea of the magnitude of that risk. There was also a recurrent belief that risk was dependent on physical resemblance to the affected relative. This factor may go at least some way to explaining the results found by Evans et al. (1993).

One of the mainstays of medical practice has to be “first do no harm.” This has been a major concern in the setting up of screening services for familial breast cancer. It is undesirable and indeed many would argue unethical to inform a woman of her increased risk if no reliable preventative or therapeutic intervention is available for the disease. When the efficacy of screening for breast cancer at a young age is, at best, unproven and the most reliable preventative measure is bilateral prophylactic mastectomy, it is of paramount importance that genetic counselling clinics do not raise anxiety levels to a state where quality of life is adversely affected. The results of most studies to date have been reassuring on this point.

Although numbers were small in the study by Green et al. (1993) and a high proportion of volunteers proved not to be at significantly increased risk, the results can be considered valid in that, at the time of interview, all women believed themselves at risk. In general, women were not unduly anxious about their own risk and were often more concerned for future generations. Peaks and troughs were observed in anxiety levels which were lowest after a negative scan result and built up as the next examination became due. Anxiety levels were also increased as the subject approached the age at which her closest relative had been diagnosed with cancer.

A further study of women at risk for ovarian cancer (Wardle et al., 1993) found that
subjects were not significantly more anxious than controls. However, those with an information-seeking coping style ("monitors") were more likely to be made more anxious by a positive scan result than those who tend to avoid unpleasant situations ("blunters"). Reassuringly, this was short-lived and even those eventually referred for surgery appeared to adapt well. In both these studies the women were self-selected in response to public advertising campaigns and may not therefore be representative of at-risk women as a whole.

What impact does knowledge of risk, anxiety and coping style have on health-related behaviours? Kash et al. (1992) found that 70% of women believed that early detection of breast cancer was possible and that they personally could be effective in this process. 94% of subjects in this study adhered to guidelines for screening mammography; those who did not had significantly higher anxiety levels. There was a negative relationship between anxiety about cancer and attendance for a clinical breast examination i.e. those who were more anxious were less likely to comply. However, breast examination by a physician was more likely to be sought by those who either perceived their personal risk as high or thought that breast cancer was a serious disease. In general those with high anxiety levels adhered less well to preventative measures including breast self-examination. Prior to attendance at a high risk clinic only 16% of women had regularly performed breast self-examination (BSE). Despite education in the technique and emphasis on its value in early detection, the figure rose only to 40% after attendance.

The subjects studied by Lerman et al. (1993) were less self-selected in that they were recruited by contacting first degree relatives of breast cancer patients rather than by publicity appealing for volunteers. In this way it was hoped that the results might be
more representative of women at increased risk as a whole. Again 72% perceived their risk as above average. 70% said that breast cancer worries did not interfere with their daily functioning. Measures of depression were comparable to the general population but scores for intrusive thoughts were rather higher. Only 16% had never had a mammogram; 65% had had a mammogram within the past year. Use of mammography was age related and was markedly decreased after the age of 50, in spite of the major contribution of age to overall risk. Factors predicting adherence to mammography were: time from diagnosis of the affected first degree relative, age, education level, employment status and levels of psychological distress. Screening practices did not appear to be related either to perceived risk or to documented risk factors. 

By contrast, Vogel et al. (1990) found that only 35% of women with a positive family history had ever had a mammogram. This did not differ significantly from those without such a history (31%). However, amongst those who perceived their risk as high (rather than simply increased) the figures were greater. Some women thought that mammography itself posed an increased risk and this might potentially have inhibited them from obtaining one. This factor seemed to be outweighed if the woman herself was at true increased risk. From the total number of reported mammograms it was clear that few, if any, of the subjects was undergoing this examination annually.

It has been proposed that adherence to mammography might follow a Fear Arousing Communications Theory (Janis and Feshbach, 1953; Kash et al., 1992). The hypothesis is that certain levels of anxiety are necessary for action; if anxiety is low there is no motivation to obtain screening and if it is too high fear of a positive result inhibits compliance. To date no studies have been able to prove this conclusively.
Other possible barriers to adherence are cost (as most studies originated in America), lack of referral by a physician, concerns about radiation and anxiety over a positive result (Lerman et al., 1993).

THERAPEUTIC OPTIONS FOR FAMILIAL BREAST CANCER PATIENTS
Given the increased risk conferred by a family history of breast cancer, what can be done to prevent it or, at the very least, to improve the prognosis once the cancer has developed? At present there would seem to be four obvious choices open to these women. The first is simply to live with the knowledge of an increased risk and do nothing further. More realistically, perhaps, she may wish to avail herself of one or more of the following:

A). Screening.
From the arguments already presented it will be appreciated that the efficacy of screening by mammography in the young age group encompassed by familial breast cancer clinic patients is at best unproven. Nonetheless, there have been reports of impalpable cancers being picked up by this modality in women as young as 28 (H. Russell, personal communication; P. Preece, unpublished data). The technique can be considered non-invasive. Some concern has been expressed with regard to the potential for increasing the benign biopsy rate (Baker, 1982) but, when combined with careful clinical assessment and further evaluation by fine needle aspiration cytology in experienced hands, this should be kept to an acceptable minimum. Image guided core biopsy of lesions may further reduce the need for formal excision (Chare et al., 1996).
B). Drug Therapy.

Tamoxifen when given as adjuvant therapy in breast cancer patients has been noted not only to prolong disease-free survival but also to decrease the incidence of contralateral breast cancers by one-third (Nayfield et al., 1991). This observation has led to a number of large randomized trials of the efficacy of tamoxifen in breast cancer prevention, with conflicting results. The largest of these, NASBP-P1 conducted in the USA, showed a 50% reduction in both invasive and in situ cancer in the treated arm (Fisher et al., 1998). In addition, those cancers which did occur in this group tended to be smaller, of lower grade and with fewer involved lymph nodes, all factors which indicate a better prognosis. Two other studies have failed to demonstrate any benefit. The first of these (Veronesi et al., 1998) may simply have been too small or included women at too low a prior risk to show a statistical difference. Also, the trial was stopped prematurely due to the drop out rate attributed to side effects of tamoxifen and follow up is too short and incomplete. The second (Powles et al., 1998) recruited women at increased risk because of a family history. Tumours in the genetically predisposed group tend to be oestrogen receptor negative. Tamoxifen appears to decrease the risk of ER+ve tumours only. Follow up for this trial was longer than for the NSABP-P1 raising the question of lead-time bias in the latter i.e. tamoxifen may be delaying tumour growth rather than affecting tumour initiation.

An international study which tries to address the questions left unanswered due to the design faults of the above trials has recently completed recruiting. Women at increased risk from a variety of factors were invited to take part in a double-blind placebo-controlled randomised trial of treatment for five years (Powles, 1992).
Women attending familial breast cancer clinics formed a large proportion of trial participants. The conclusions of this International Breast Intervention Study will not be available for a number of years but interim results are promising (see Discussion page 131).

C). Prophylactic Mastectomy.

No controlled trials of mastectomy in the prevention of breast cancer have been carried out. It would seem logical to assume that removal of the breast tissue would remove the risk. However, this has not entirely been true of ovarian carcinoma for which the results of prophylactic surgery are available. At the time of the study reported in this thesis, following oophorectomy the quoted residual risk of ovarian cancer was around 5%, arising either in peritoneal epithelium or from ovarian cells seeded in the peritoneum (Tobacman et al., 1982, Piver et al., 1993). This figure may turn out to be even higher because prophylactic oophorectomy was carried out in the absence of molecular studies and therefore some of the women involved would have been non mutation carriers who were not actually at increased risk. However, more recent data appear reassuring. Rebbeck et al. (2002) found a significantly reduced risk of ovarian or coelomic epithelial carcinoma in women with disease-associated germline mutations in BRCA1 or BRCA2, with a hazard ratio of 0.04.

Even the most skilled of surgeons cannot guarantee to excise 100% of the breast tissue in 100% of operations. Such mutilating procedures have the potential for profound psychological consequences and should not therefore be undertaken without careful consideration of all the other options. Nevertheless, women at particularly high risk may prefer an end to uncertainty rather than living with the daily fear of
developing breast cancer.

A small series of prophylactic mastectomies carried out in high risk women in Stockholm, Sweden revealed invasive carcinoma in 2 out of 10 patients and in-situ disease in a further 2 (Sandelin, unpublished data). A larger prospective study (Hoogerbrugge et al., 2003) showed pathological lesions known to increase the risk of malignancy (e.g. atypical ductal hyperplasia) in 57% of prophylactic mastectomy specimens. None of these had been detected pre-operatively by either clinical examination or imaging.

Schrag et al. (1997) have calculated the theoretical gain in life expectancy from various interventions in BRCA1 or BRCA2 mutation carriers. The years of life gained decrease with increasing age at the time of prophylactic surgery for two reasons: firstly, with increasing age there is less chance of cancer developing as the result of genetic susceptibility and secondly there are fewer years of normal life expectancy remaining. The model used to make these calculations made assumptions about the effectiveness of screening and early detection that are not upheld in clinical practice. It also assumed uniform efficacy for all classes of familial risk which is inaccurate (Moller et al., 2002). Nevertheless, clinical data are now emerging to support at least some reduction in breast cancer risk in women from the higher risk families who have undergone oophorectomy (Rebbeck et al., 2002). This study, conducted in known BRCA1 or 2 mutation carriers, demonstrated a 96% reduction in ovarian cancer incidence and a 53% reduction in breast cancer in women undergoing bilateral oophorectomy.

The expected gain with various estimates of efficacy of prophylactic mastectomy were also calculated. If mastectomy is considered 97% effective at preventing
subsequent breast cancer, 4.8 years of life-expectancy are gained; if only 25% effective, this reduces to less than one year. However, the authors base their calculations on the unproven premise that intensive screening in itself has the potential for substantial increase in life-expectancy, thereby reducing the apparent overall gain from prophylactic surgery.

Hartmann et al. (1999) have followed up a large series of prophylactic mastectomies from the Mayo clinic. In total there were 1039 high risk women (mean age 43) representing 15,660 person years of follow-up. A highly significant reduction in breast cancer risk was found. Calculations of expected numbers of breast cancer were made from the risk profiles of the individual women, 69% of whom underwent prophylactic mastectomy because of a family history. Of 81 cancers expected in these women, only 10 actually occurred (p<0.001). A more recent prospective study in women known to carry BRCA1 or 2 mutations confirms this risk reduction, although the follow-up period of only three years is very short (Meijers-Heijboer et al., 2001).

GENETIC TESTING
The ethical issues surrounding and the potential social and psychological consequences of testing for genetic susceptibility to breast cancer have been the subject of much debate amongst clinicians and others involved in the care of these patients. Until recently, such testing could only be performed by linkage analysis in a small subset of families in whom sufficient specimens could be traced to make the procedure technically feasible. Even then it should be emphasised that individuals have to be made aware of the limitations of this technique, which is subject to at least 5% error rate, depending on the linked markers chosen for analysis, the prevalence of
sporadic cases within breast cancer families, and the figures for gene frequency and penetrance used in the calculations. However, most of the families who have undergone testing in this manner have been involved with research in this field over a long period of time and are thus usually well informed and highly motivated. Their reactions to genetic testing may not therefore be typical of the wider population of those at risk because of a family history.

Because of the above factors, very few data are available on this subject in the world literature. What has been published tends to relate to the experience with individual families and most studies are descriptive only. Certain conclusions can be inferred from the study of other adult-onset genetic diseases, such as Huntington's disease, for which more detailed data are available but caution must be exercised in drawing too close comparison between these and familial breast cancer for several reasons. Firstly, no therapeutic intervention is available to delay the onset of or halt the progress of Huntington's disease which inevitably leads to a slow and unpleasant death. On the other hand, those at high risk for breast cancer can opt for prophylactic mastectomy or in the unfortunate event of developing breast cancer can expect an average cure rate of 50%. Secondly, Huntington's is fully penetrant, whereas around 20% or more of carriers of BRCA1 mutations may never develop breast cancer over their lifetime (Ford et al., 1994).

One report by Biesecker et al. (1993) from the United States aimed to give the likely impact of genetic testing for BRCA1 mutations on the individual, the family and the health services. They describe a single family in which 35 individuals were offered testing for BRCA1 by linkage analysis. Women were counselled according to an approved protocol which allowed them time to absorb the facts and come to an
informed decision. One woman who had already undergone prophylactic mastectomy some years previously and who was subsequently found not to be a carrier accepted that she had made the best decision in light of the information available to her at the time. One other, who was already scheduled for surgery, cancelled this immediately on hearing that she was not a carrier. Most female carriers opted for prophylactic mastectomy. The most frequent psychological sequelae were feelings of guilt (that an individual did not carry the mutation whilst a close relative did) and responsibility (towards gene carriers and members of future generations who were at risk of inheriting the mutation from a carrier parent). Only immediate consequences of the test are mentioned in this report, although the authors indicate that they intend to conduct more long-term follow-up studies of this aspect.

Tyler and Harper (1983) described their experience with families at risk of Huntington's disease and their attitudes towards genetic counselling. It was not one of the primary aims of the study to determine the possible uptake of genetic testing in this group. However, they do comment that the figure was relatively low when compared to other similar studies. Non-directive counselling was given in two stages; the first fairly general and the second giving more specific information. The majority of participants were social class 3. The family itself was the greatest disseminator of information but the facts passed on were often inaccurate. Interestingly, for a disease with such devastating symptoms and consequences, few said that they would modify their family size in response to their risk.

In other studies of Huntington’s disease using linked markers for predictive testing, most participants (85%) understood the principles and limitations of the technique very well (Mastromauro et al., 1987). 66% of respondents in this study said that they
would have the test, the chief reason given being to end uncertainty. Only 12% would make use of prenatal testing were it to be offered to them. This study however had a very low overall response rate of 42% and it may be that there was some self-selection in that it may have been those who perceived themselves at highest risk of a positive result who declined to participate.

Another study has looked at actual uptake of testing for Huntington’s disease rather than simple intention to be tested (Bloch et al., 1989). In the first 16 months after a test becoming available, only 12.6% of those at risk known to be eligible for testing had registered. This is obviously much lower than anticipated but it may be that others will register, given time. All those who did come forward in the earlier part of the programme were educated to a fairly high standard and were psychologically well adjusted. They may therefore represent a group who tend to seek out health information and are emotionally healthier.

Retrospective analysis of all tests performed in the UK to date again showed the uptake to be less than predicted (Tyler et al., 1992). Women were more likely to go through with testing than men, in a ratio of 2:1. This may again reflect the greater involvement of women with health care matters in general and reproductive decisions in particular. The authors of this survey anticipated that the demand for testing would increase once the gene had been isolated and tests no longer had to rely on linked markers.

Few data are as yet available on women’s attitudes to genetic testing for breast cancer susceptibility and what measures they would be prepared to take to prevent breast cancer, should the test prove positive. Some researchers (Lerman et al., 1994) have found very positive attitudes but the individuals concerned often belong to large
families at particularly high risk which have been part of research studies for many years and thus may not be representative of the majority of at-risk women. Julian-Reynier et al. (1996) found that 87.7% of women would ask for a genetic test if one were to become available. However, their patients included a significant number who were already affected with breast cancer. If these women were excluded from the analysis, 95.8% of healthy women said they would wish a genetic test and 90.8% of them would inform their relatives about the availability of the test.

The overwhelming majority (96.6%) expected that having the test would automatically afford them access to improved health surveillance and screening facilities. Drawbacks to a positive test were seen as the anxiety this would provoke and the changes in lifestyle which it might necessitate. In the event of a negative test, 52% stated that this should not alter the intensity of screening and many felt that the recommendation to give up such intensive screening would be the main drawback to having the test in the first place.

ETHICAL ISSUES

The possibility of testing for mutations in cancer susceptibility genes raises many ethical and legal questions. Unlike most other health care measures, carriage of a gene mutation has implications not only for the individual undergoing the test but also for the wider family circle who are at risk of having inherited the same mutation. Should these individuals also have access to the test results and is it ever ethical under these circumstances to breach a patient's confidentiality? What about interested third parties such as employers and life insurance companies? The Nuffield Council on Bioethics
(1993) has attempted to address these issues and has set out the following recommendations, although recognising that these are subject to change in the light of new genetic developments.

Individuals should be fully informed of the results of genetic screening and should be encouraged to share these with others who might benefit from the information or to allow health care professionals to do so on their behalf. In exceptional circumstances where such permission is refused and when it is considered imperative that another family member has the right to know, both the law and professional guidelines allow for the individual’s desire for confidentiality to be overridden.

Employers should not normally have access to the results of genetic testing except where a positive result may have implications for the safety of either the individual being tested or other employees. This clause should not apply to inherited cancer susceptibility. The situation as regards life insurance is more complex. At present British insurance companies adhere to a policy of not requiring any genetic tests as a prerequisite for obtaining insurance and it is to be strongly desired that this situation continue (Policy statement by Association of British Insurers, February 1997). As yet there is no legislation on the subject. A moratorium on genetic test results in the future may apply only to policies of moderate size. Also, where a genetic predisposition can readily be established from standard questions about family history of a disease, insurance companies can and do load or refuse policies because of high risk calculated on this information alone.
PATIENTS AND METHODS

In October 1992 a clinic was set up in Edinburgh to provide genetic counselling and screening to women with a family history of breast cancer. Such women had previously been seen as part of the symptomatic breast services supplied by the Edinburgh Breast Unit which currently sees 6,000 new out-patients and 450 new breast cancer cases per annum (Mr. J.M. Dixon, personal communication). Others were seen by general surgeons with an interest in breast disease working in district general hospitals. Based on population statistics, it was estimated that about 500 females between the ages of 25 and 50 in the south-east of Scotland (total female population approximately 500,000) may carry a dominant gene for breast cancer (Prof. C.M. Steel, personal communication). At least an equal number would also be at increased risk of the disease because of their family history, although in this group no definite genetic cause could be implicated.

Funding was obtained from the Scottish Hospitals Endowment Research Trust (SHERT) to run the clinic for three years. Within this period it was hoped to establish the demand for counselling and screening services for this group of women, to compile a register of those at true increased risk of developing breast cancer and to provide a subset of families suitable for and willing to take part in ongoing molecular genetic research projects. Approval was granted by the local ethics committee.

REFERRAL CRITERIA

All women entering the study were initially referred either from a hospital out-patient clinic or by their general practitioner. The clinic was not run on an open access basis. General practitioners in the Edinburgh area were identified from the database
maintained by the South-East Scotland Breast Screening Service and were mailed an information package outlining the familial risks of breast cancer and inviting appropriate referrals. The criteria employed were:

1. First degree relative with bilateral breast cancer or breast and ovarian cancer at any age.
2. First degree relative with breast cancer diagnosed under 50 years or ovarian cancer under 55 years.
3. Two first degree relatives with breast or ovarian cancer diagnosed at any age.
4. Male first degree relative with breast cancer at any age.
5. A cancer family history which is of concern to both the patient and the referring clinician although it does not match any of the above categories.

A total of 300 GPs were sent this information package (Appendix 1).

It is now recognised that these criteria may have been too “liberal” resulting in the referral of too many women who were not at significantly increased risk.

CLINIC FORMAT

The clinic was established with a multidisciplinary team of staff consisting of members with training in genetics, oncology and breast surgery. Psychological assessments were conducted by Dr. Ann Cull, ICRF Department of Psychological Medicine, Western General Hospital. A full-time genetics research nurse was employed to co-ordinate the running of the clinic. The facilities of the South-East Scotland Breast Screening Programme were used together with the expertise of the radiologists employed by this service and the established mechanisms for further assessment and investigation of any women found to have a clinical or
mammographic abnormality.

At the first clinic visit a detailed family history was taken by trained staff using a proforma designed and modified over many years experience in this field by registry staff at the MRC Human Genetics Unit. By using this method, information on a standard set of first and second degree relatives was gathered in each case. Written informed consent was also obtained to access hospital records and for the withdrawal of a blood sample for genetic research purposes (Appendix 2). Basic genetic principles as applied to breast cancer were discussed at this stage as was the possibility of future genetic testing for a small subset of selected families and individuals. Information was collected on known breast cancer risk factors such as age at menarche, parity, age at first pregnancy, previous benign breast disease, history of ovarian surgery and use of exogenous hormones including the oral contraceptive pill. All women had their breasts examined by one of two breast surgeons (E. Anderson or E. Smyth).

All cases of cancer reported by the proband were confirmed as far as was possible by reference to hospital casenotes, cancer registration data and death certificates (see below for further detail). A case conference was held involving all members of the multidisciplinary team and a risk estimate arrived at for each woman on an individual basis (see Risk Estimation, page 60).

Women were then invited to a review appointment when the individual risk estimate was discussed and a screening protocol recommended. Where considered desirable, mammography was performed at this appointment. For those judged to be at sufficient risk, two-yearly mammographic screening was begun at 35 years of age and continued to age 40. Thereafter mammography was performed on an annual basis.
until the woman became eligible for the National Breast Screening Programme (NHSBSP) which she was strongly advised to attend from age 50 years. In a few instances, where age of onset in the family suggested an increased risk beyond the age of 50, special arrangements were made to carry out breast screening at intervals of 18 months, between the examinations offered under the NHSBSP. All women enrolled in the screening programme had their breasts examined annually and were instructed in breast self-examination.

Psychological assessments were undertaken at regular intervals throughout this process (see page 63 for detail).

FAMILY HISTORY CONFIRMATION.

All family history proformas were carefully examined by a single member of staff (E. Smyth) and extensive efforts made to confirm all reported cancer cases by at least one of the methods outlined below. In addition, a set of pedigrees thought likely to provide information suitable for subsequent linkage analysis was selected for verification and extension by the MRC Registry workers (R deMey and A Fordyce).

1. Hospital Casenotes.

This was the preferred mode of confirmation where at all possible. In most instances histopathological verification of the diagnosis was available. Copies of the pathology report were made for future reference, providing a valuable source of material for genetic analysis, particularly from deceased family members when a blood sample (which is the preferred source of DNA) obviously could not be obtained. Some tumours were diagnosed on clinical grounds alone, especially in elderly patients treated by non-surgical means. Such verification was recorded as a separate category.
Those confirmed by fine needle aspiration cytology were grouped with the histologically confirmed tumours.

The main obstacles to verification by casenote review were inaccuracy of details (such as dates of birth) provided by the proband and the practice of many hospitals of destroying casenotes after a given time interval. This could frequently be offset by obtaining notes from other departments such as radiotherapy which often keep casenotes, complete with copies of pathology reports, in perpetuity.

2. Death Certification.

The MRC Human Genetics Unit Registry is accorded privileged access to the Registrar General for Scotland's records of births, deaths and marriages. This allows family pedigrees to be traced in considerable detail, sometimes starting with only outline information. The purposes of such detailed pedigree work are three-fold:

a) Confirmation of cancer diagnosis and site by death certificate.

b) Provision of accurate dates of birth where these could not be supplied by the proband (which in turn increases the success of attempts to trace relevant hospital and cancer registration records).

c) Expanding selected family trees for genetic linkage purposes.

3. Cancer Registration Data.

The Information and Statistics Division of the NHS Common Services Agency holds data on all cancers diagnosed in Scotland since 1958. This includes information on histological verification and type as well as site of tumour, date of diagnosis and hospital where treated. Due to ethical considerations, data can only be released on deceased individuals and thus this method was reserved for cases which could not be verified by any other means. Nevertheless, cancer registration was in several
instances capable of supplying sufficient detail to enable pathology specimens to be obtained for research purposes even when the relevant hospital records had been destroyed.

Cancer registration data sometimes also supplemented or corrected death certificate information since post-mortem findings are incorporated into the former.

RISK ESTIMATION.

Detailed scrutiny of individual pedigrees revealed that they almost all fell into one of several categories.

1. Those in which breast cancer predisposition could clearly be seen to be inherited in autosomal dominant fashion.

2. Those in whom only distant relatives were affected and who could be presumed to be at no appreciable increased risk.

3. Those in whom the observed pattern of cancers in the family followed that of a recognised cancer-family syndrome such as Lynch Type II (Lynch et al., 1973) or Li-Fraumeni (Li and Fraumeni, 1969).

4. The majority of families whose risk must be considered moderately increased but in whom no clear hereditary pattern can be established. This is a very heterogeneous group which includes those with a single affected first degree relative for whom widely accepted risk estimates are readily available (Houlston et al., 1992) and many others in which calculation of a risk estimate is at best a very inexact science.

It is for the last group that the case-conference was found to be invaluable in arriving at an assessment of risk, in that difficult cases were discussed in detail by the entire clinic team and a consensus arrived at once differences of opinion had been resolved.
In this way it was hoped that the women themselves would be spared any confusion arising from conflicting information given by different clinicians. In most cases the figure was arrived at by estimating the probability that a given individual was a mutation carrier and multiplying this by the estimated penetrance of the putative breast cancer genes (Iselius et al., 1991; Houlston et al., 1992).

Risks were communicated verbally to the patients as a residual lifetime risk, expressed as a ratio of the population residual lifetime risk calculated from the patient’s age. For example, a lifetime risk of 4 times the population lifetime risk.

SCREENING PROTOCOL.

Women with risk estimates of at least two times the population risk of developing breast cancer by age 70 (that is, 20% or more lifetime risk) were considered at true increased risk of the disease and were assigned to one of two groups; either to begin mammographic screening immediately or, if younger than 35, to have their details registered to commence screening when they attained this age. Where a close relative had developed breast cancer under the age of 40 screening was commenced 5 years earlier than the youngest diagnosis of breast cancer in the family. This regime was established on the basis that

1). Sensitivity of breast tissue to radiation is strongly age-dependent, so that regular mammography should be delayed until age 35 where possible (Law 1997).

2). Age of onset of familial breast cancer tends to “breed true” within families, so that those with a relative affected at a very early age are themselves judged to be at risk from a similar (or even earlier) age. This comes from epidemiological data showing concordance among relatives for age of onset of breast cancer. (The same is
not so clear for ovarian cancer.)

Mammograms were performed two-yearly until the age of 40 and annually from 40 to 50 years. This regime was established on the assumption that even in a genetically predisposed population, breast cancer is more common over 40 than under this age and that at this age the breast tissue is also more clearly visualised and less sensitive to the theoretical carcinogenic effects of ionising radiation (Law, 1997; Kerilkowske et al., 1993). The initial screen was by two-view lateral oblique and cranio-caudal mammograms with subsequent screening rounds employing single oblique views alone (Wald et al., 1995). The same radiographer performed almost all of the examinations. Mammographic examinations were continued regardless of the breast parenchymal pattern identified on the initial films.

Films were read independently by two radiologists as for the National Breast Screening Programme. Any abnormality identified was followed up by further clinical examination by an experienced breast surgeon and subsequent investigation by whichever means was considered most appropriate, such as ultrasound examination, fine needle aspiration cytology or biopsy if clinically indicated.

PSYCHOLOGICAL ASSESSMENT.

All women attending were invited to participate in a psychological assessment by completing questionnaires either at the time of the clinic visit or supplied to them by post. This part of the study was designed and supervised by Dr. Ann Cull, Department of Psychological Medicine, Western General Hospital, Edinburgh. The aims of the psychological assessments were to determine women’s prior knowledge of breast cancer risk and mechanisms of coping with this, their health-related...
behaviours and their attitudes to any possible future developments in screening and prevention. A major additional concern was that attendance at the clinic should not adversely affect anxiety levels or general well-being, or interfere with daily living, and thus these modalities were also measured.

Established standardised psychological questionnaires were used together with others designed “in-house” to answer queries pertaining to breast cancer in particular. Two weeks prior to the first clinic visit women were mailed a number of questionnaires to be completed at home and returned when they attended the clinic. These consisted of:

(i) Risk estimation. Women were asked to select from a number of options expressed as a probability i.e. 1 in 2, 1 in 10 etc., the lifetime risk for the population in general and their own lifetime risk of developing breast cancer.

(ii) General Health Questionnaire. (GHQ-30) This was used to screen for clinically significant levels of psychological distress and dysfunction (Goldberg and Williams, 1988). The manual for this instrument provides extensive comparative data derived from population surveys which are well validated.

(iii) Health-related Locus of Control Scale (Wallston and Wallston, 1978). This assesses the extent to which women attribute their health to internal (i.e. own behaviour) or external (e.g. doctors) factors

(iv) Miller Behavioral Style Scale (Miller, 1987) has been designed to assess the propensity of individuals to seek out ("monitors") or avoid ("blunfers") information about threatening events.

(v) Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) was used to measure anxiety proneness (trait) and current levels of generalized anxiety (state).
The former part of the questionnaire was administered by post prior to the clinic visit with the latter part being completed at the time of attendance but before any contact with a clinician.

Appended to these were several questions regarding their own health practices with particular reference to breast self-examination [(BSE) (Appendix 3)].

At the review appointment, three months later, and after being seen by a member of the medical staff to discuss the calculated personal risk estimate and screening recommendation together with any other issues raised, the state anxiety and risk estimation questionnaires were repeated.

Three months following the review appointment, patients were mailed a questionnaire assessing their attitudes to breast care and future interventions (Appendix 4). A reply paid envelope was provided for its return. Questions related to BSE and barriers to BSE such as fear of finding a lump, beliefs about breast cancer screening, and what action a woman would be prepared to take in order to prevent breast cancer in the future e.g. screening, drug therapy, prophylactic surgery.

GENERAL PRACTITIONER ASSESSMENT OF SERVICE

After a period of two years of clinic operation, a questionnaire was mailed to the same 300 GPs who had been sent the initial information package (Appendix 5). These asked whether they were aware of the existence of the clinic, if they had referred any women to it (together with their estimate of how many) and whether they were satisfied with the service provided. Space was included for free comment if desired but the aim was to keep the questionnaire as short as possible given the amount of administrative paperwork which most GPs have to deal with. A pre-paid
envelope was included for the return of the questionnaire.
FINDINGS

The clinic was initially funded for three years commencing October 1992 and this period forms the basis of the present study population. The sample for analysis has been limited to new referrals attending during the first 21 months of operation to enable complete 3 month and annual follow-up data to be collected on the entire cohort.

EVALUATION OF DEMAND FOR SERVICE

During this time 429 women attended the clinic. Four were already affected with breast cancer but had requested referral in order to obtain information about risk on behalf of other family members. These four have been excluded from all subsequent analyses. The median age of the 425 women included for analysis was 39.9 years (S.D. 9.4; range 17-71 years). It should be noted that only referrals of women under 50 were invited but an appointment was not denied to any woman outwith this age group if she or her GP were concerned about her family history.

Distribution of Social Class

Social class is usually determined by occupation. However, in this data set occupation was inconsistently recorded and varied between the patient’s own occupation and that of her spouse. The Carstairs Deprivation Score was therefore utilised as an approximation to social class. This score allocates a deprivation category to each postcode sector in Scotland and is based on a number of well validated variables such as car ownership, male unemployment and overcrowding. (Carstairs and Morris, 1991). The population is divided into equal categories which
are numbered 1 to 7 from least to most deprived. Combining DEPCATS 1 with 2 and 6 with 7 generates 5 categories almost equally represented in the Scottish population (Scottish Health Statistics) approximating quite well to the “conventional” five social classes.

Three women could not be allocated a score because they reside outwith Scotland. Of the others 146 (34.3%) fell into category 1; 91 (21.4%) were category 2; 85 (20%) were category 3; 89 (20.9%) were category 4 and only 14 women (3.3%) fell into category 5. Thus over 50% of the clinic attendants were considered to come from the least deprived two fifths of the population.

Whilst breast cancer is predominantly a disease of less deprived women, there is an over-representation of categories 1 and 2 in the women attending the clinic when compared to breast cancer cases in the population as a whole and a very striking deficit of the most deprived category (Figure 4).

Sources of Referral

Most patients (344; [80.4%]) came from Edinburgh and Lothian district. 22 (5.1%) came from the Borders region, 10 (2.3%) from Central region and 44 (10.3%) from Fife. Only 8 patients travelled from further afield and most of these were relatives of women who had already attended the clinic.

Overall, 40.2% of referrals came directly from GPs and 59.8% from secondary sources such as hospital out-patient departments, well-woman and family planning services. Patients from the Edinburgh area were slightly less likely to have been referred by their GP (39.2%) compared to those from other areas (44%). However, this trend is not statistically significant ($X^2=0.648; 0.25<P<0.5$).
GENETICS CLINIC REFERRALS AND BREAST CANCER CASES BY DEPRIVATION CATEGORY

FIGURE 4.
There was no difference in deprivation category between GPs and other sources of referral ($X^2=2.59; P=0.27$). In other words, those in social classes 1 and 2 were no more or less likely to have been referred by their GP than those in social classes 4 and 5.

Numbers of women coming from outside the Edinburgh area are too small to allow any meaningful analysis of potential differences in deprivation category between regions.

The pattern of referral has however changed with time. In the initial period after setting up the clinic, only 25% of referrals came directly from GPs with the figure being around 75% at the end of the study period (1995/6). Within the Edinburgh area, the Edinburgh breast unit (EBU) was the single largest source of referral, referring 199 patients (GP referrals 135). All these patients had attended a symptomatic breast clinic and, on routine questioning, had been found to have a positive family history. It is acknowledged that an unspecified proportion of these women may have attended primarily because they were aware of the increased risk conferred by a family history and that any symptoms they were experiencing may have been a secondary and relatively minor consideration, simply providing a legitimate and acceptable reason for referral to a specialist unit. The number of women to which this might apply cannot be assessed.

Screening Recommendations

Women who were calculated to be at two or more times the population lifetime risk (i.e. >20%) for developing breast cancer were considered eligible for mammographic screening. Thus, 30.6% of women were discharged after the initial assessment
because they did not meet this criterion. For the remainder there were two possible courses of action:

1. Names of those who were at increased risk but who could not yet benefit from screening were placed on an "at-risk" register. This group was comprised mainly of women under the age of 35 years whose total lifetime risk was at least two times the population risk but whose risk in the next few years would be relatively low and insufficient to warrant the use of mammography at this early age. A small proportion of women in this category were placed on the register because examination of their family tree could not give enough information to determine a risk estimate but it was felt that future development of genetic testing may be helpful. In total 18.8% of women were placed on the "at-risk" register.

2. Those women who met the criteria of increased risk and were aged 35 to 50 years were offered immediate mammographic screening. (Some women under the age of 35 were included in this group because their risk was felt to be exceptionally high in that some family member(s) had been affected at a particularly young age). This was the largest group, forming 50.6% of the total.

When analyzed by source of referral, the two largest sources of referral (GPs and Edinburgh Breast Unit: EBU) were equally good at identifying those at true increased risk (median lifetime risk 21.6% for GPs; 24.0% for EBU). No comment can be made about other sources of referral as numbers in these groups were small. Table 5 shows the number of women from various referral sources and their calculated median lifetime risks.

Examining distribution of risk according to source of referral and geographical region of residence revealed no difference between GPs and other referral sources within
<table>
<thead>
<tr>
<th>Source of referral</th>
<th>No. of women referred</th>
<th>Median estimated residual lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBU</td>
<td>199</td>
<td>24.01</td>
</tr>
<tr>
<td>GP</td>
<td>172</td>
<td>21.60</td>
</tr>
<tr>
<td>Relative</td>
<td>19</td>
<td>26.76</td>
</tr>
<tr>
<td>Hospital clinic</td>
<td>16</td>
<td>27.80</td>
</tr>
<tr>
<td>BSP</td>
<td>8</td>
<td>15.00</td>
</tr>
<tr>
<td>FPC</td>
<td>7</td>
<td>28.14</td>
</tr>
<tr>
<td>Genetics Dept.</td>
<td>2</td>
<td>30.00</td>
</tr>
<tr>
<td>Familial ovarian cancer clinic</td>
<td>2</td>
<td>34.50</td>
</tr>
<tr>
<td>Self</td>
<td>3</td>
<td>17.67</td>
</tr>
</tbody>
</table>

**TABLE 5. Risk according to source of referral.**

EBU  Edinburgh Breast Unit  
GP   General Practitioner  
BSP  Breast Screening Programme  
FPC  Family Planning Clinic
Edinburgh or surrounding districts outwith the city boundaries (Table 6). None of the women referred by the breast screening programme were at sufficiently increased risk to require additional screening, mainly because they were all over 50 years of age. Three women had directly requested assessment without referral by a doctor; none of these was at increased risk.

Clinical Findings

All women presenting to the clinic had a detailed breast examination carried out by one of two experienced female breast surgeons. Only 37 women (8.8%) had a palpable abnormality. All such abnormalities were followed up by the appropriate means employed in symptomatic breast clinics i.e. mammography and/or ultrasound, FNA cytology, excision biopsy.

Women for whom it was thought to be of potential benefit were offered mammography at the second appointment. A total of 164 mammograms were carried out at this stage; that is, 76.3% of those eligible. At least part of the discrepancy is accounted for by women’s previous history of mammography; if this had been carried out within the previous twelve months it was not repeated at this stage. Instead, the patient was registered to be recalled when the annual mammogram was due. A further 117 mammograms were performed at the annual review appointment.

The difference in the figures for initial and annual mammograms is due to the different patterns of screening employed for women aged over 40 years and those aged 35 to 40 (see page 62).

Recall following detection of a mammographic abnormality was required for 6 (3.7%) women at the initial review and a further 3 (2.6%) at the year 1 stage. Further
TABLE 6. Median estimated residual lifetime risk (%) of breast cancer according to source of referral and geographical location.

<table>
<thead>
<tr>
<th>Source</th>
<th>GP Referrals</th>
<th>Other sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh</td>
<td>21.68</td>
<td>24.60</td>
</tr>
<tr>
<td>Other postal districts</td>
<td>21.33</td>
<td>22.93</td>
</tr>
</tbody>
</table>
mammographic views with or without ultrasound confirmed the benign nature of these impalpable abnormalities. No-one required to be investigated by stereotactic FNA biopsy although this facility is readily available at the Edinburgh Breast Screening Centre.

Twelve ultrasound examinations were performed; 9 at the initial review and 3 at annual follow-up. Eleven FNAs were carried out at the first visit and 10 at annual review. All were for palpable abnormalities. Only 4 in total proceeded to excision biopsy. All lesions proved to be benign; no breast cancers have been detected in the study population to date. (A total of 9 cancers have subsequently been diagnosed in women in this cohort, although none were in the period covered by this report).

Future Demand: Identification of Additional Individuals at Risk

Examination of the pedigrees of women attending the clinic identified a total of 324 other women who could potentially benefit from genetic counselling and screening. Their ages ranged from 2 to 63 years and potentially all will require screening, either immediately or in the future. In terms of more immediate requirements for mammographic screening, 202 of this group are currently aged over 35 and a further 59 over 30 years. Thirty-nine women would be eligible for screening under the National Breast Screening Programme by virtue of being aged 50 years or over. Eighty-one of the women under 50 years thus identified are known to be in receipt of screening; 44 at the local Edinburgh clinic and 37 at similar clinics throughout the country. The screening practices of the remaining 121 in the age group eligible for screening are unknown.

Most families in which additional individuals were considered “at risk” contained
only one such woman. Only 14 families had 4 or more additional relatives at risk.

Other Characteristics of Clinic Population.

All women were asked about known breast cancer risk factors such as parity, age at first live birth, use of oral contraceptives and previous breast disease or biopsy.

1. Parity.

77.3% of women (mean age 41.5 years) had had children. Mean age of the remaining 22.7% nulliparous women was 34.3 years. Amongst the parous group mean number of pregnancies was 2.1 and age at first live birth 24.9 years. Nulliparous women in the cohort can therefore be considered to represent a group who have either chosen to remain nulliparous or who will begin child-bearing at a significantly later age; both factors which are known to increase the risk of subsequent breast cancer (Harris et al., 1992) although this may in fact be different for BRCA1 carriers (Jernstrom et al., 1999).

2. Use of Oral Contraceptives.

Only 60 women of the 428 (14.3%) had never used the oral contraceptive pill (OCP). Amongst those who had previously taken it and now stopped (66.3%) average duration of use was 5.5 years (range 0.2-28 years; 95% C.I. 1-14 years). For current users (19.3%) mean duration was 8.4 years. Mean age at first birth did not differ according to contraceptive use, being 24 years for never users, 25 for previous users and 26 for current users.

Parous women tended to have used oral contraceptives for longer than nulliparous women (5.5 v. 5.1 years for previous users; 9.4 v. 7.0 years for current users). This however may simply be a reflection of the older age of the parous group (Table 7).
<table>
<thead>
<tr>
<th></th>
<th>Never users</th>
<th>Previous users</th>
<th>Current users</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parous</td>
<td>0</td>
<td>5.5</td>
<td>9.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>0</td>
<td>5.1</td>
<td>7.0</td>
<td>4.9</td>
</tr>
<tr>
<td>TOTAL</td>
<td>0</td>
<td>5.5</td>
<td>8.4</td>
<td>5.2</td>
</tr>
</tbody>
</table>

TABLE 7. Median years of oral contraceptive use according to parity.
3. Previous Breast Biopsy.

64 women (15.2%) with a mean age of 44.9 years had previously undergone biopsy of benign breast lesions. Most were for conditions such as fibroadenoma but 4 showed severely atypical epithelial hyperplasia, a recognized risk factor for subsequent breast cancer and one which is multiplicative when combined with a positive family history (Dupont and Page, 1985). Two of the women with this pathological condition also had a positive family history whilst the other two did not. The mean age of those who had never had a breast biopsy was 38.9 years. As might be expected, the likelihood of undergoing breast biopsy therefore increases with age.

EVALUATION OF CRITERIA FOR ENROLMENT: ASSESSMENT OF PUBLISHED REFERRAL CRITERIA

Due to the rapidly increasing referral rate, particularly from the primary care sector, and the consequent workload upon the clinic it was thought that the referral criteria may be too “loose” i.e. they allowed the inclusion of too many women who were not in fact at true increased risk. It was hoped to amend these criteria in order to exclude such patients from the outset without excluding any of those at genuine risk of familial breast cancer. The referral criteria employed by the Edinburgh clinic were thus compared to those published by the already well established familial breast cancer clinic in Manchester which runs along similar multidisciplinary lines (Evans et al., 1994; [Table8]).

The unconfirmed family histories reported by the women themselves were examined
<table>
<thead>
<tr>
<th><strong>EDINBURGH REFERRAL CRITERIA</strong></th>
<th><strong>MANCHESTER REFERRAL CRITERIA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative with bilateral breast cancer or with breast and ovarian cancer.</td>
<td>First degree relative with breast cancer &lt;40 years.</td>
</tr>
<tr>
<td>First degree relative with breast cancer diagnosed under the age of 50 or ovarian cancer under the age of 55.</td>
<td>First degree relative with breast cancer &lt;50 and close relative on same side of family with breast, ovary, colon, endometrial carcinoma or sarcoma &lt;50 years.</td>
</tr>
<tr>
<td>At least two first degree relatives with breast or ovarian cancer diagnosed at any age.</td>
<td>First degree relative with breast cancer 50-65 years and close relative on same side of family with breast, ovary, colon, endometrial carcinoma or sarcoma &lt;50.</td>
</tr>
<tr>
<td>Male first degree relative with breast cancer.</td>
<td>First degree relative with double primary tumour (breast + ovary, colon, endometrium or sarcoma). At least one tumour before age 50 and breast cancer before age 65.</td>
</tr>
<tr>
<td>A “cancer family” history causing concern although it does not fit any of the above categories.</td>
<td>Dominant history of breast cancer (&gt;4 cases breast and/or ovary, same side of family, any age).</td>
</tr>
<tr>
<td>History of related malignancy in mother or father (cancer of colorectum, ovary, endometrium or sarcoma) before age 50 and at least one of their first degree relatives developed breast cancer before age 50.</td>
<td>Two or more cancers of related types (breast, ovary, colon, endometrium or sarcoma) in close relatives on father’s side, but not necessarily including father, with one cancer diagnosed before age 50.</td>
</tr>
</tbody>
</table>

**TABLE 8.**
for goodness of fit to these two sets of referral criteria. The unconfirmed rather than confirmed version of the family history was used in this analysis as the former would have been the version on which the original referral was based.

Goodness of fit to the two sets of referral criteria was correlated with the calculated risk estimate (calculated on the verified version of the family history).

In total 53.9% (230) fulfilled the Manchester criteria whilst 69.6% (297) fulfilled the Edinburgh criteria.

The range of calculated risk estimates was the same for both groups i.e. from no increased risk up to 6 times that of the general population over a lifetime. Median lifetime risks were 25% for those fulfilling the Edinburgh criteria and 30% for those fulfilling the Manchester criteria.

Taking the Edinburgh criteria first, 87.5% of those who met the criteria were deemed at sufficient lifetime risk to require mammographic screening either immediately or at a future date dependent on present age. Only 73.8% of those who did not meet the initial referral criteria were able to be reassured and discharged. Thus, over one quarter of those women who would not have been sent an appointment had the referral criteria been applied strictly, were actually considered at greater than two times the population lifetime risk and therefore eligible for screening: 20% immediately and 6.2% at a later date.

The same analysis applied to the Manchester criteria shows that again 86.9% of those who met the criteria for referral were considered at truly increased risk according to the method of risk estimation used in our clinic (see page 60). However, almost half (47.7%) of women who would not even have received an appointment had the Manchester criteria been applied strictly, were at sufficient risk to be enrolled for
screening: 36.5% immediately and 11.2% at a later date.

Combination of the data into those who met neither set of referral criteria, those who met either the Edinburgh or the Manchester criteria or those who met both are presented in Tables 9 and 10. Table 11 details the action taken in relation to criteria fulfilled.

In general, a higher percentage (93.9%) of those who met both sets of criteria was considered eligible for screening. Applying both sets of referral criteria also allowed a greater number of women to be discharged when they did not fulfil either (80.4%). However, there remains a huge “grey area” amongst those women who fitted only one set of referral criteria in that some women not at true increased risk would have attended for assessment and others at genuinely increased risk would have been denied an appointment.

EVALUATION OF ACCURACY OF FAMILY HISTORY DOCUMENTATION.

Information on family history was obtained from 429 probands belonging to 397 separate families. Where probands were first degree relatives of each other, their reported family histories were combined and the most accurate version of the combined information used for comparison with confirmed family histories. If probands were second or third degree relatives of each other they were analysed as separate families, as they usually attended the clinic independently and shared only one side of the ancestry (either maternal or paternal).

Three probands were excluded from further analysis in this part of the study because they came from large families who had previously taken part in linkage analysis studies and whose knowledge of their own family histories might therefore be
<table>
<thead>
<tr>
<th>MANCHESTER CRITERIA</th>
<th>EDINBURGH CRITERIA</th>
<th>No (22.7%)</th>
<th>Yes (7.7%)</th>
<th>Total (30.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>97</td>
<td>33</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100 (23.4%)</td>
<td>197 (46.1%)</td>
<td>297 (69.6%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>197 (46.1%)</td>
<td>230 (53.9%)</td>
<td>427 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 9. Referral criteria fulfilled.

<table>
<thead>
<tr>
<th>MANCHESTER CRITERIA</th>
<th>EDINBURGH CRITERIA</th>
<th>No (9.0)</th>
<th>Yes (12.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>14.0</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20.7 (20.0)</td>
<td>30.0 (30.0)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 10. Mean (median) lifetime risks according to referral criteria fulfilled.
### TABLE 11. Decision to screen, place on at-risk register or discharge subdivided for referral criteria fulfilled.

All figures are given in percentages.

<table>
<thead>
<tr>
<th>Referral Criteria Fulfilled</th>
<th>Discharge</th>
<th>Register</th>
<th>Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both</td>
<td>6.1</td>
<td>26.9</td>
<td>67</td>
</tr>
<tr>
<td>Manchester only</td>
<td>54.5</td>
<td>15.2</td>
<td>30.3</td>
</tr>
<tr>
<td>Edinburgh only</td>
<td>25</td>
<td>19</td>
<td>56</td>
</tr>
<tr>
<td>Neither</td>
<td>80.4</td>
<td>3.1</td>
<td>16.5</td>
</tr>
</tbody>
</table>
expected to be exceptionally good. The 4 probands already affected by breast cancer were also excluded as they could well have biased recall of other affected family members.

In all, 390 separate families were included in this analysis giving a total of 5262 first and second degree relatives. More distant relatives were not considered as information on such individuals was not recorded prospectively or systematically.

Data on 5 mothers and 10 fathers were missing. 462 sisters and 398 brothers were reported. This gives an average family size of 3.2 children for the probands’ generation. A total of 1134 aunts, 1115 uncles and 1388 grandparents (expected 1560) were reported. That is, information on 11% of grandparents was unknown to the probands. The average family size in the parental generation (mother, father, aunts, uncles) is calculated as 3.9 children.

Provision was made for reporting and confirmation of up to three primary cancer sites per relative. No individual was reported to have more than three different cancers.

The initial aim of the checking process was to confirm cancers reported by the proband and to enable tracing of tissue specimens for genetic analysis in selected families. A systematic search was not made for cancers not reported by the proband. Nevertheless, a number of such tumours were identified. The drawing up of detailed family trees in selected families from the Registrar General’s central records located 107 individuals who had been omitted from the pedigree by the proband. Only 5 of these were known to be still alive at the time of the study. The remainder were either deceased or could not be traced further (Table 12). Eleven cancers were diagnosed in this group, only one of which was in a living individual. The sites were colon, liver,
TABLE 12. Cancers identified in relatives not known to proband.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Alive</th>
<th>Dead</th>
<th>Not Known</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4</td>
<td>65</td>
<td>27</td>
<td>96</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gall-bladder</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5</td>
<td>75</td>
<td>27</td>
<td>107</td>
</tr>
</tbody>
</table>
gall-bladder and lung. No breast or ovarian cancers were identified in relatives unknown to the proband.

Sixty-nine cancers in 67 individuals were under-reported by the probands. Forty-eight relatives who had been reported as disease free, were found to have cancer. In two cases the individuals concerned had two separate primaries, neither of which had been recorded by the proband. The remaining 19 under-reported cancer cases represent individuals who were reported as having a single primary but in whom the checking processes revealed additional cancer sites.

Conversely, there was some over-reporting of cancers in other individuals. Eighty-one people were said to have been affected by cancer who had none. A further 23 had one less primary than reported and 3 individuals were reported as having 3 separate primaries where only one existed.

These figures apply only to cases where the available checking mechanisms were able definitively either to confirm or refute the presence of cancer. Where extensive searching failed to reveal the reported tumour, the cancer was recorded in a separate category of “unable to confirm or refute.”

Accuracy in First Degree Relatives.

A total of 1625 first degree relatives were identified. 579 primary cancers were reported in 519 first degree relatives. The checking processes confirmed 586 cancers in this group. These numbers include those cancers reported which could, after extensive searching, neither be confirmed nor refuted. For risk assessment purposes such cancers were given “the benefit of the doubt.” The actual number to which this applies cannot be calculated retrospectively from the data recorded. Overall, the
checking processes identified 1.2% more cancers in this group than those reported.

Accuracy in Second Degree Relatives.

This group includes 3637 individuals. 701 primary cancers were reported; 727 were confirmed. Thus there is again some under-reporting of cancers in second degree relatives with 3.7% more cancers being identified following the checking procedures. The same criteria apply to those cancers which could neither be confirmed nor refuted which were again given the “benefit of the doubt” for risk estimation purposes.

Accuracy by Cancer Site.

The figures were analyzed for breast cancer separately since this was the cancer site of prime interest to both the clinic team and the patients. It might therefore be expected that patients would have more accurate knowledge of a history of this cancer in any of their relatives. 652 unilateral and 54 bilateral breast cancers were reported. 605 unilateral and 44 bilateral cases were recorded after checking (including those neither confirmed nor refuted; n=169). The checking process identified 8 unreported unilateral breast cancers. There were no unreported bilateral cases although 2 cases were reported as unilateral which were in fact bilateral. In general there was more over- than under-reporting of breast cancers with 47 individuals reported as affected who did not have breast cancer (although 19 of these did have cancer of another site) and a further 10 reported as bilateral which were in fact unilateral. There were no cases reported as bilateral who had no breast cancer.

The positive predictive value of the confirmatory processes for breast cancer is
therefore 0.903. If those cases which could not be confirmed or refuted are considered true positives this gives a PPV of 0.93; if all are assumed to be false positives, the PPV is 0.669.

Pattern recognition is important in identifying familial cancer syndromes in which further genetic testing may be available either currently or in the future. A number of other cancer sites associated with breast cancer in certain familial cancer syndromes were selected for calculation of accuracy. These were ovary and prostate (BRCA1), uterus (Lynch type II; see p.26) and colon (Lynch type II and BRCA1). The results are shown in Table 13. For all sites, the accuracy was greater where the cancer was the first or only primary. The figures for breast as second primary refer to those cases where the disease was bilateral. In general, the most common cancers in these families were also the most accurately reported. The accuracy for endometrial cancer was particularly low although gynaecological cancers as a group were reported more accurately than average for other sites excluding breast.

Methods of Confirmation

Cancers were confirmed by reference to case notes, pathology records, autopsy reports and death certificates. If all these avenues failed and the case concerned had been resident in Scotland at the time of treatment and was now deceased, the Scottish Cancer Registry was contacted. Pathological confirmation either from histopathology of the primary tumour or post mortem data was considered the most informative method of confirmation as this provided a laboratory reference number, enabling stored material to be obtained for genetic analysis and other allied collaborative research projects such as those carried out under the auspices of the European Breast
### TABLE 13. Accuracy by reported cancer site (% of cases confirmed according to whether cancer was 1st or 2nd primary).

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>1st Primary</th>
<th>2nd Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>90.3</td>
<td>64.7</td>
</tr>
<tr>
<td>Ovary</td>
<td>78.9</td>
<td>-</td>
</tr>
<tr>
<td>Colon</td>
<td>60.8</td>
<td>57.1</td>
</tr>
<tr>
<td>Prostate</td>
<td>37.5</td>
<td>-</td>
</tr>
<tr>
<td>Endometrium</td>
<td>16.7</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>73.1</td>
<td>55.5</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Casenotes</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>417</td>
<td>88</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>449</td>
<td>116</td>
</tr>
</tbody>
</table>

TABLE 14. Methods of confirmation for all cancers

Means of confirmation of cancer cases are shown in Table 14. Where more than one method of confirmation was obtained for a given cancer, only the most useful source of confirmation was considered in this analysis. For example, some cancers were recorded clearly on death certificates but were also confirmed from cancer registration data. As the latter gives a date on which treatment commenced which can be useful in tracing pathological tissue specimens even when the casenotes have been destroyed, it is considered a more useful level of confirmation.

In several cases, cancers were confirmed from casenotes which had been omitted from either death certificates or cancer registration data. In such cases the appropriate authorities were informed in order to amend central records. The number of cancers to which this applies was not recorded but it was small.

Effects of Confirmatory Process on Action Taken

As has been reported above, there were relatively few inaccuracies of reporting of breast cancer. In only 11 families did such inaccuracies alter the risk estimate sufficiently for the proband to be calculated at low risk and discharged from further follow-up. In none of the other families where inaccuracies were identified did these alter the decision to offer mammographic screening. In 18 cases the risk estimate was revised downwards and in a further 6 it was increased, although never by more than a single increment either way (e.g. from 2x population to 3x population but never 2x to 4x). Ten of the decreases in risk estimate were due to unilateral breast cancers being reported as bilateral. In none of the remaining 15 families in which inaccuracies were
identified did these alter the numerical risk estimate because the cancers inaccurately reported occurred in more distant relatives, at more advanced age or on the opposite side of the family to that from which hereditary predisposition was apparent.

Ovarian cancer inaccuracies, on the other hand, invariably altered the action recommended to the proband. Three ovarian cancers were reported where none existed thus obviating the need for referral for ovarian cancer screening. A further three women were offered referral to the ovarian cancer screening clinic on the basis of previously unknown cancers of this site being identified within their families. Although the probability of a BRCA1 mutation in these families is significantly altered by these results, in no cases did this alter the decision to screen for breast cancer, but it may have implications for the possibility of future genetic testing in these individuals.

Pattern recognition is an important aspect of cancer family syndromes such as those associated with BRCA1 and 2 and the Lynch type II syndrome. Seventeen previously unknown colon cancers were identified only one of which was in a first degree relative. A further 15 colon cancers in second degree relatives were refuted. Only 2 previously unknown uterine cancers were identified and 3 were refuted although two of these individuals were already affected by breast cancer. Thus the overall risk estimate remained unchanged although clues as to the particular gene involved would be different. Four cancers (2 reported as colon and 2 unspecified) were confirmed as primary pancreatic, a site which can be associated with BRCA2 mutations (Breast Cancer linkage Consortium, 1999). Prostate cancer has an increased relative risk in BRCA1 families (Ford et al., 1994); six hitherto unknown cancers of this site were identified and a further five refuted, again all in second degree relatives.
EVALUATION OF PSYCHOLOGICAL IMPACT

Characteristics of Women Attending

1. Prior knowledge of risk. A small minority of women estimated their own risk at the extremes of the scale provided to them with 4% believing it inevitable that they would get breast cancer and 6% setting their risk as <1:100. Sixty-three percent set their own risk at 2 or more times the general population risk (the level considered appropriate to offer screening) whilst 31% considered their risk increased to a lesser degree. Somewhat surprisingly for those attending a “high risk” clinic, 7% estimated their risk below that of the general population.

2. Accuracy of personal risk estimate prior to counselling. Relative to the calculated risk estimate, 14% of women grossly overestimated their risk by a factor of 2 or more (“overestimators”) and 31% underestimated to the same degree (“underestimators”). The remainder fell between these limits and are designated “close estimators”. Only 7% were exactly accurate in their initial risk estimate.

3. Anxiety status. The sample as a whole exhibited a higher mean trait anxiety level than that derived from women in the general population (Knight et al., 1983) (two sample t-test: t=4.9; P<0.001) but not significantly different from scores reported in women attending for breast screening (Morris and Greer, 1982).

Baseline state anxiety scores collected at the first clinic visit were significantly higher than the data from the general population (two sample t-test: t=3.4; P<0.001) but significantly lower than the data from the screening
clinicsample (two sample t-test: \( t = -8.0; \, P < 0.001 \))

4. Psychological distress (GHQ-30). Mean score for women attending our clinic was 4.5 (S.D.=6.2) which is similar to scores from age-matched respondents in a general population survey in the UK (Cox et al., 1987). Thirty percent of our women scored above the cut-off recommended for identifying case-level distress i.e. those who would benefit from additional counselling and training in methods of stress reduction. There was no difference in baseline stress levels or indeed in case-level distress amongst over-, close and underestimators.

Impact of Counselling

1. Personal risk estimate. Data were collected immediately post counselling and categorized according to accuracy of baseline risk estimate (i.e. over-, close and underestimators). Over estimators showed significantly lower risk estimates after counselling \((z=5.69; \, P<0.0001)\) but still tended to overestimate relative to the counselled risk \((z = -2.60; \, P<0.001)\). Twelve women persistently overestimated their risk by a factor of greater than two despite counselling.

As a group, underestimators reported significantly higher risks after counselling \((z= -8.01; \, P<0.0001)\) but they continued to underestimate relative to the counselled risk \((z=7.37; \, P<0.0001)\). Women with close estimates at baseline tended to report lower estimates after counselling \((z=1.74; \, P=0.08)\).

2. Anxiety status. After counselling, state anxiety levels were significantly lower
than baseline scores for the same women (paired t-test: t=3.1; P<0.003). Examined separately, under-, close and over-estimators all showed a reduction in state anxiety scores after counselling but the difference was statistically significant only for overestimators (t= -2.38; P<0.03).

3. Psychological distress. Mean GHQ-30 score after counselling (mean=3.1, s.d.=4.9) was significantly lower (paired t-test: t=3.6; P=0.0004) than that at baseline. A key concern was that if counselling changed women’s estimate of their risk (especially if it increased) this would cause psychological distress. There was no evidence of an association between change in risk estimate and change in GHQ scores (r=0.04; P<0.5).

EVALUATION OF PREVIOUS HEALTH RELATED BEHAVIOURS AND COPING STYLE (MILLER BEHAVIORAL SCALE)

Breast Self Examination.

Despite being sufficiently motivated to attend a familial breast cancer screening clinic, 10.2% of women admitted to never having examined their own breasts. Common reasons expressed were fear of finding a lump or never having been shown how to examine their breasts properly.

The majority of women did examine their own breasts; 30.3% at least occasionally, with 20.6% performing BSE every few months and 29.1% once per month. Only a small number of women examined themselves more frequently with 2.9% examining more than once per week.
Breast Examination by a Physician.

Fifty per cent of women had attended their GP or a hospital clinic or both for breast examination. For half of these, the frequency of visits was less than once per year. Less than 10% were attending a physician more than twice per year for breast examination.

Mammography.

228 (53.3%) women had previously obtained mammograms. From the recorded data it is impossible to determine how many of these were simply screening examinations and how many were performed as part of the investigation of breast symptoms such as pain. Women who had undergone mammography were older than those who had not (mean age 44.6 years v. 34.2 years). This may be a reflection of the fact that most breast clinics do not routinely carry out mammography on women under the age of 35 except for very strong clinical indications.

If the group of women under 35 years is taken separately, only 12 had previously had a mammogram while 110 had not. Mean ages in these two subgroups were similar. A much higher proportion (73.5%) of women over 35 had obtained mammograms. Similarly, within this group ages of those who had and those who had not did not differ significantly.

Coping Style

The Miller Behavioral Scale (1987) assigns individuals to the category of “monitor” (information seeking) or “blunter” (denial of threat) depending on their methods of coping with threatening events. The abbreviated form used in this study has been
well validated (Steptoe, 1989). Each individual is scored for monitoring (M) and blunting (B). The value M-B assigns those with a positive score to “monitor” and those with a negative score to “blunter.”

Coping style of the current cohort was analyzed to see whether this might dictate how they came to the clinic, what screening procedures for breast cancer they may have taken up already and whether clinic attendance had any adverse effects on either group in terms of increased anxiety. In all, 407 complete data sets were available for these analyses. Monitors constituted 283, bluters 57 and 67 individuals scored neutral. Because of the large difference in numbers in each category, the data were analysed in a number of ways. The Mantel-Haenszel test quoted here takes into account the differing numbers in each group and also factors in those who scored neutral.

If it is assumed that those who were referred by their GP largely represent a group of women who have sought out help (in relation to familial breast cancer) for themselves (which may not in fact be a valid assumption) it might be expected that there would be a larger proportion of monitors in this group. Overall, there was no significant difference between monitors and bluters for source of referral ($X^2=0.32; P=0.85$). However, if deprivation category was also taken into account in this analysis bluters were much less likely to have been referred by their GP if they came from the more deprived sectors (categories 4 and 5) of the population ($X^2=7.33; P=0.02$). There was no difference in referral source for monitors across all deprivation categories ($X^2=1.2; P=0.54$).

The previous health screening behaviours of breast self examination, breast examination by a physician and mammography were also analyzed for coping style.
There was no difference between monitors and blunters for previous breast self examination \( (X^2=2.11; \ P=0.71; \) Mantel-Haenszel test for linear association\(=0.22; \ P=0.64) \). Monitors were slightly more likely to have sought out examination by a physician but again this failed to reach statistical significance \( (X^2=9.24; \ P=0.06; \) Mantel-Haenszel test\(=3.14; \ P=0.08) \). Figures for previous mammography gave similarly non-significant results \( (X^2=3.51; \ P=0.48) \). However, this last statistic is likely to be particularly unreliable as obtaining mammography depends on so many other factors such as the age of the patient, the clinical findings and the opinion of the consulting physician.

Impact on Compliance with Clinic Recommendations.

Overall the non-attendance rate was low. Sixteen women \( (3.9\%) \) were given their risk estimate at the initial visit and were not required to return. Most of these were not considered at increased risk but some were relatives of other patients whose risk estimates had previously been calculated but who did not yet require screening because of their young age and who were therefore placed on the at-risk register. Of the remainder, 69 women \( (16.7\%) \) defaulted from follow-up. For this purpose a non-attender is defined as a woman who failed to attend two consecutive appointments or who cancelled an appointment without making another and who had failed to do so within 3 months.

Effect of Anxiety Status

None of the women who thought it inevitable that they would develop breast cancer
defaulted from follow-up appointments. Whilst non-attendance in other groups was generally quite low, there appeared to be a relationship between attendance and perceived risk in that the higher a woman initially believed her own risk to be, the more likely she was to come back for subsequent appointments (Kruskal-Wallis test $H=15.24; P=0.001$). No such relationship existed when the calculated risk estimate was used rather than the patients’ perceived risks ($P=0.34$).

Risks for those who defaulted varied from 10 to 50%, with a mean of 22.4%. However, almost two-thirds of this group had calculated risks less than 20% which, for many, would not have qualified them for entry into the screening programme and for others put them at the lower end of the eligible range. Thus few women missed out on screening because of their non-attendance ($n=29$).

The more anxious a woman is, the more likely she may be to either seek out reassurance or avoid all screening including breast self examination. Trait anxiety, i.e. anxiety proneness, did not predict for those who had or had not previously attended a physician for breast examination (Mantel-Haenszel test for linear association $=0.23; P=0.63$). Having had previous examination by a physician or mammography made no difference to state anxiety levels at the time of clinic attendance (Levene’s test $F=0.02; P=0.89$).

Breast examination was carried out at the second clinic visit. However, those who had never had this procedure showed no difference in change of anxiety level over those who had (Levene’s test $F=0.11; P=0.74$). Similar results apply to mammography. Change in anxiety status from first to second visits did not show any association with prior screening practices (Levene’s test $F=1.63; P=0.20$).
EVALUATION OF SERVICE BY GENERAL PRACTITIONERS

Those general practitioners \( (n=300) \) who had been informed of the clinic by letter at its inception were mailed a questionnaire pertaining to their usage of the service (Appendix 5).

The initial information letter contained details of the rationale for this new service together with guidelines as to the type of women who should be referred (Appendix 1). Bearing in mind the amount of paper work which GPs have to deal with, the questionnaire was kept deliberately brief. They were asked whether they had ever heard of the service and, if so, from what source. They were also asked to estimate how many women they had personally referred and whether they (the GP, not the patient) were satisfied with the service provided. Space was left for free text comments if so desired.

273 general practitioners returned the questionnaire. A second mailing to non-responders had been planned but was considered unnecessary given the excellent initial response rate (91%). 73 GPs (27.5% of responders) said they had no knowledge of the clinic. Of the remainder, 113 (57.1%) had first heard of it from the information sent to them; 24 (12.1%) learned about it through other patients; 36 (18.2%) were given information on a GP study day and 52 (26.3%) had been informed by various other sources or could not remember. Some GPs \( (n=50) \) had learned of the clinic from more than one source. Thus the above figures add up to greater than 100%.

Eighty-four (42.4%) GPs had heard of the clinic only via sources other than the information package sent to them. Twenty of these heard from other patients or
relatives of women who had already attended and who were seeking referral for themselves.

Accuracy of recall of numbers of patients referred is likely to be unreliable. Nevertheless, GPs were asked to estimate from memory how many patients they had referred. Forty had not as yet referred any patients although they did know of the clinic’s existence. The majority (136) thought they had referred between 1 and 5 patients, 16 had referred 6 to 10 and only 6 GPs claimed to have referred more women than this. From our own clinic records only 6 GPs had in fact referred more than 3 patients. However, at the time the questionnaire was sent out there was a 6 month waiting list for an appointment so that GPs may have referred patients who had not yet been seen. Such referrals may account for at least part of the discrepancy.

One very interesting question which cannot be addressed from these figures is whether those GPs who had referred more patients were any more accurate at picking out those at true increased risk than those who had referred relatively few. This question will require a much larger cohort to give a reliable answer.

Only 12 GPs were not satisfied with the service they and their patients received. Most of the comments related to the long waiting time for the initial consultation rather than to any specific criticisms of the way in which the counselling and screening process was handled. Most family doctors said they would be happy to use the service in the future, including those who had not known about it before receiving the questionnaire. Only 5 thought that they would not refer patients in the future, expressing the view that they were content with the more traditional line of referral to hospital out-patient departments.
DISCUSSION

Familial breast cancer was recognized by the Ancient Romans. Interest in the subject and possible causes including inherited predisposition and shared environmental factors has waxed and waned over the centuries (Broca 1886; Macklin 1959). Only in the late twentieth century has the technical expertise to identify specific genes become available. Mammographic screening and prophylactic mastectomy are also relatively recent innovations and their efficacy is as yet unproven although preliminary results are promising (Hartmann et al., 1999; Meijers-Heijboer et al., 2001; Moller et al., 2002).

EVALUATION OF DEMAND FOR SERVICE

The population in South-East Scotland has generally been considered to be relatively stable in terms of movement into and out of the area. It might be supposed therefore that there would be a finite number of families at risk within the region and that, after a period of time, no further high risk women would be coming forward. However, new referrals are continuing at a steady rate even after the end of the study period reported here and those considered at sufficient risk to warrant screening continue to constitute around 75% of referrals, a finding replicated around the country (Wonderling et al., 2001). In addition, new families with an autosomal dominant pattern of inheritance continue to make up between 5 and 10% of referrals, which is important as members of these families are more likely to carry a detectable mutation in one of the major breast cancer genes.

One possible explanation for this steady stream of new at-risk families is that women present at varying time intervals following the diagnosis of breast cancer in a
relative. Figures to support this are not available from the present study but it has previously been shown that motivation to obtain screening diminishes as time following diagnosis in a relative passes (Lerman et al., 1993). There seems to be an optimum time interval after diagnosis for referral. If this is too soon, the patient will be too anxious about her relative to attend; if too late, she may have lost the incentive. Media publicity and comments from friends or relatives can also serve as a reminder and precipitate a visit to the family doctor for reassurance.

Distribution of Social Class

The Carstairs deprivation score (Carstairs and Morris, 1991) allocates individuals to categories according to postcode, based on factors such as car ownership, overcrowding, male unemployment and low social class and is therefore not directly equivalent to social class. However, it is a well validated approximation and is in wide use by many authorities including the Scottish Cancer Registry (Sharp et al., 1993) thus allowing for easy and direct comparisons with these data.

The predominance of deprivation categories 1 and 2 amongst the patients attending may reflect greater awareness of risk in these groups but as breast cancer also affects predominantly these classes the finding is not entirely unexpected. However, examination of figure 4 (p. 68) shows that the relative excess of categories 1 and 2 is greater amongst women attending the clinic than amongst breast cancer patients. This is similar to the findings of others (Julian-Reynier et al., 1996; Moatti et al., 1990) that higher socio-economic status is a determinant of attendance at genetics clinics. Those who are more educated tend to look after their own health better and to seek out screening and preventative services.
In the future, measures need to be put in place to ensure that the more disadvantaged women in the “at risk” population are not denied access to potentially beneficial counselling and screening facilities. These could take the form of publicity campaigns in areas accessible to such groups including GPs’ waiting rooms, sports centres and social clubs. The potential problem with such a publicity campaign is that it will continue to reach the better educated social class I and II women and be ignored by those from classes IV and V. Many general practitioners now ask routine questions about family history of both benign and malignant disease when a new patient registers at the practice. In this way susceptible individuals can be identified and referral to a specialist clinic offered if desired. When so doing, however, it must be borne in mind that, although evidence is now emerging to support screening in these women, the benefit is as yet unproven and has to be balanced against the risks of increased psychological distress (see p.44) and radiation to the breast (Law, 1997). A small study (Women’s Concerns Study Group, 2001) found that family history was mentioned in 3.7% of all consultations with a GP and that clinicians were 6.6 times more likely to raise the subject than was the patient. Extrapolating these figures to average GP list size and rates of consultation would mean that each GP would see 4 or less patients with a significant family history per year.

Sources of Referral

The pattern of referral has changed significantly over time from only 25% coming directly from GPs at the beginning of the study to a corresponding 75% at its end. It is accepted that some women referred from other sources such as hospital out-patient departments may have initially attended because of worries about their genetic risk.
and simply saw breast symptoms as a legitimate method of gaining referral, particularly as mammography is not available on the NHS to asymptomatic women under the age of 50.

In addition, the GPs themselves have come to recognise the value of the clinic from the information sent to them at the outset, GP study days and from those who have either used the service already or have relatives or friends who have done so (see under “Evaluation of Service by General Practitioners; p.120).

There was a tendency for those residing within Edinburgh to be less likely to have been referred by the GP although this did not reach statistical significance. Perhaps this can be explained by the ready access to a major tertiary referral breast unit afforded to Edinburgh city GPs.

With the rapid rate at which the field of cancer genetics is advancing, the primary care sector cannot be sufficiently equipped to provide specialist risk counselling. However, GPs in this series were as good as other sources including a tertiary referral breast unit as picking out those at increased risk. This is in agreement with the findings of others, that the number of referrals of women in low risk categories was significantly less when GPs were supplied with information packs and referral guidelines. The quality of information contained in the referral letter also improved. (Watson et al., 2002). GPs now also ask about family history when met with a request for HRT. However, as we are primarily concerned with women under the age of 50, this should not significantly affect the referral rate to clinics such as the one described here.
Screening Recommendations and Clinical Findings

Only 50.6% of women were eligible for immediate mammographic screening but a further 18.8% were also considered at significantly increased risk although they have not yet reached an age where mammographic screening should begin (35 years). However, all 429 women had a clinical breast examination by a breast surgeon. This aspect of the service is labour intensive and thus costly. Less than 10% had a clinical abnormality requiring further investigation so there was therefore relatively little use of other diagnostic services such as ultrasound, FNA and open biopsy. Rates of recall for impalpable mammographic abnormalities (3.7%) were considerably lower than those for the national breast screening programme (7.3%; NHSBSP report, 1993).

Perhaps a little unexpectedly, given the risk profile of the women attending, no cancers were detected in this cohort during the study period. Other familial breast cancer screening clinics in Scotland have cancer detection rates in line with those expected. In one clinic an impalpable cancer was detected by mammography in a patient aged only 28 years (P. Preece, personal communication).

Several reasons may be postulated for the absence of breast cancer detection in the current study group:

(i) Relatively small numbers. In a three year period one might have expected to diagnose 6 cancers per 1000 women screened in a young at-risk population. This equals detection rates in the prevalent (i.e. first) round of screening for the over 50s screened via the National Breast Screening Programme. Thus, in a sample of 425 women less than 3 cancers would have been expected, and the results are therefore explicable on the grounds of small numbers alone.
(ii) The majority of the early referrals in this cohort came from hospital sources and not directly from primary care. Patients with prevalent cancers would therefore have been seen by a specialist unit already and would not have come to the familial screening clinic.

(iii) Over 50% of all patients and 73.5% of those aged over 35 years had previously obtained mammograms from other sources. Any abnormalities seen would again have been investigated and treated prior to clinic attendance. The cohort presented here equates better to incident screening rounds under the NHSBSP in which detection rates are more in the order of 3 per 1000.

(iv) The follow-up period of the present study (3 years) is too short.

Points (ii) and (iii) are likely to be related and together probably constitute the main reason for the lack of cancer detection in this cohort at the time of conclusion of this study. Subsequently, however, 9 cancers have been detected in this cohort, 2 of whom (one a 35 year old BRCA1 mutation carrier) have died of their disease. (Joyce Campbell, personal communication). One of those who died had her cancer detected on her second (annual) mammogram, suggesting that she may have had a particularly fast growing and aggressive tumour type. The interval between being enrolled in the screening programme and the diagnosis of a cancer varied from 1 to 9 years. Ages at diagnosis ranged from 35 to 58 years.

In terms of radiation risk associated in the screening of young women with a family history, Law (1997) supports a radiation dose 15-20% greater than that required for the screening of postmenopausal women in the National Breast Screening Programme. In practice this is well inside the uncertainty limits for dose estimation and therefore for cancer induction. Provided that screening takes place within
dedicated screening centres (as was the case for this study) which meet the quality control requirements of the NHSBSP, mammography in young women is thought to be safe.

The interval cancer rate (cancers presenting between screening examinations) and false negative (missed cancer) rates for familial breast cancer screening programmes will need to be audited carefully. However, it is to be hoped that, with the frequency at which these women are screened, this rate should be extremely low indeed (Moller et al., 1999; 2002; Macmillan et al., 2000)

Other Characteristics of Study Population

Figures for previous benign breast biopsy rate in an age-matched sample of the general population are not available. This has in any case changed over time with greater confidence in cytology as a diagnostic modality and more conservative management of lesions such as fibroadenomata. No comment can therefore be made about the characteristics of the study population reported here in relation to the general population in this respect.

Figures for oral contraceptive use do not appear to differ markedly from those for an age-matched population (Department of Health statistics, 1998). Current use of the OCP in women aged 16-49 years was 19% overall, being highest in younger age groups (48% for 20-24 year olds and 34% for those aged 25-29) and declining dramatically after the age of 40. These figures are limited to current use and do not address “ever” use in the older subgroups or duration of use. The latter two factors are equally important in women attending a family history risk clinic.
Few data are available as to the exact risk incurred by oral contraceptive use in those already at increased risk due to hereditary factors. What data are available relate to those with known mutations in the major breast cancer genes. Narod et al. (2002) found no associated increased risk in BRCA2 mutation carriers but there was a moderate increase in risk for BRCA1 mutation carriers. This increase was greater if the OCP was taken for more than five years, use under the age of 30, and if taken prior to 1975 (when oestrogen content of the available formulations was relatively higher). Heimdal et al. (2002) state that the risks are probably similar to general population risks for familial breast cancer as a whole. The increased risk in BRCA1 carriers decreases with time since last use.

Future Demand

There has been no decline in the rate of new referrals over the study period and indeed in subsequent years. The demand for screening and other diagnostic services rises as subsequent screening rounds take place, those on the “at-risk” register become eligible for mammography, new referrals are added and scrutiny of pedigrees identifies other at-risk individuals. On the whole, this last group amounts to one individual for each proband thus doubling the numbers in the long-term. It is acknowledged that many of these are as yet very young (i.e. in their teens) and it will be some considerable time before they make use of the clinic.
EVALUATION OF CRITERIA FOR ENROLMENT

The evaluation of the criteria for enrolment indicates that no perfect set of guidelines for referral can be assembled. The Edinburgh criteria employed at the time of this study were less restrictive than the published Manchester criteria in that a greater proportion of women met the former (69.6% v. 53.9%). None-the-less, numbers of women calculated to be at two or more times the population lifetime risk were the same whichever set of criteria were applied. The range of risks was the same in both groups, although the median lifetime risk was greater in those who fulfilled the Manchester criteria.

Of concern is that almost half of the women who did not meet the Manchester criteria for referral were deemed eligible for screening in our clinic. Similar methods of risk assessment are used in both centres. This observation could therefore mean either that the Manchester criteria are too restrictive or that the Edinburgh threshold for offering screening is too low. The Edinburgh criteria were designed for ease of use by general practitioners who have only a short consultation with each patient and have insufficient time and training to take a detailed family history. The Manchester criteria on the other hand are more difficult to apply but concentrate on recognised familial cancer syndromes. The major difference however is in the group of women with only a single affected first degree relative: in Manchester that relative has to be diagnosed under the age of 40 whilst in Edinburgh this was 50 years. The Edinburgh criteria have subsequently been modified in line with the Manchester criteria in this respect, and are now superseded by Scottish national guidelines (Scottish Executive Health Department.) One mechanism to cut down on the number of low risk women being seen is for patients to submit their family history on a standardised proforma.
prior to a clinic appointment, allowing risk to be assessed and those not at sufficiently increased risk informed by letter. Each family history still needs to be formally assessed by the multidisciplinary team, but since 25% of all referrals fall into this low risk category (Wonderling et al., 2001), at least one step is removed from the process and clinic time can be devoted to those in the higher risk categories. This is now how all family history clinics in Scotland operate. The development of computer programmes to assess risk may make this process more rapid and have the advantage that they can be updated relatively readily, as new genetic knowledge accumulates. However, early experience with one such programme, BRCAPRO, (Euhus et al., 2002) has shown that, although the computer model was as accurate as trained genetic counsellors at predicting the probability of a mutation and the associated risk, it could not replace the human aspects of the consultation and should be used as an aid to counselling, rather than replace any steps in the process.

EVALUATION OF ACCURACY OF FAMILY HISTORY DOCUMENTATION

The first step in assessing risk of any familial disease is documentation of the family history. Obviously, if accurate advice is to be given to the individual, this history must also be accurate. All of the histories in this study were recorded on a standardized proforma at a face-to-face interview with a clinician asking systematically about both maternal and paternal first and second degree relatives and thus hopefully keeping omissions to a minimum. This is confirmed by the fact that out of a total of 5262 first and second degree relatives, only 107 were not known to the probands and were identified by the subsequent checking processes. The vast majority of these (102) were deceased which may be the reason they had been
overlooked by the proband. It is impossible to discern from the collected data how many were truly unknown to the proband and how many were simply forgotten at the time of the clinic visit.

It should be emphasised that a no systematic search was made for cancers not reported to the clinician. Nonetheless, there was some under-reporting of cancers which was greater for second degree than for first degree relatives (3.7% v. 1.2%). These figures are most probably an under-estimate but a systematic search for cancers not reported by the proband would involve very time-consuming (and consequently costly) drawing up of pedigrees via the Registrar General’s records. Even then, information on cancer diagnoses would be obtainable for deceased individuals only, bearing in mind new confidentiality clauses with respect to cancer registration data.

It is traditionally accepted that women tend to have greater knowledge of what goes on within the family circle than men and that they also know more about their female relatives than their male ones. This is borne out in this study in that twice as many fathers’ diagnoses as mothers’ were unknown to their daughters although the numbers of both were very small. This may be a reflection of the fact that women were often surprised to learn that breast cancer susceptibility genes can also be inherited through the paternal line and thus they may have concentrated more on finding out about the maternal side of the family. Indeed, one woman had even been told by her GP that breast cancer could not be inherited from her father’s side of the family. This issue evidently requires greater information and education.
Accuracy by Cancer Site

There was a general tendency to over-report breast cancers, perhaps as an attempt to gain attention or to ensure that screening would in fact be offered. Confusion sometimes existed about whether a case was unilateral or bilateral. This is an important distinction when assessing risk, as bilateral cases are more likely to be genetic than unilateral breast cancer arising at a similar age (Anderson and Badzioch, 1985). Proportionally there was more over-reporting of bilateral cases than unilateral but no-one was reported to have bilateral cancer who was completely free of the disease. Confusion may have existed in the proband’s mind between bilateral and unilateral cases if the affected relative had for example had a second operation for a recurrence in the same breast. It is also be possible that surgery for benign conditions may have been misinterpreted as being for cancer, especially in an era when cancer was “not spoken about.”

The much greater accuracy of reporting of breast cancers when compared to other cancer sites may be due to patients being more focused on this disease or may be a reflection of more strenuous efforts on our part to confirm or refute breast and ovarian cancers compared to the others. Although the latter is a real possibility, fairly extensive efforts were made to trace all cancer cases (in order that patterns indicative of specific cancer family syndromes might be recognized), and it is not therefore thought to be a major contributor to the observed differences.

Age of onset of breast cancer in this data set of families was generally younger than, for example, colon or prostate cancer. This may be a factor in ensuring greater accuracy of records. The better knowledge of families which women tend to have may be another factor in ensuring the accuracy of reporting of a condition which
predominantly affects females. Ovarian cancer was less accurately reported as relatives often identified the correct body cavity but the wrong primary site. Nevertheless, it was still the second most accurately reported cancer site.

Family Structure
The above analyses were carried out on the confirmed version of the family structure. This is just as important as the accuracy of cancer reporting for assessment of risk. Figure 5 shows an example of the reported and confirmed versions of the pedigree of one of the clinic patients. The proband (indicated by the arrow) had reported that two of her sisters had developed breast cancer at the ages of 35 and 42 years (Figure 5a). Tracing of the family via the Registrar General’s records showed that the proband was in fact the illegitimate daughter of her eldest unaffected “sister” and the woman she believed to be her mother who had also been affected by breast cancer was in fact her grandmother (Figure 5b). Since her biological mother is still alive and unaffected by breast cancer at the age of 70, the proband’s risk is lower than would have been estimated on the unconfirmed version of the family history. Such major changes to the family structure obviously raise ethical issues as to how much detailed information should be given to the patient and how it should be presented (see p.123). Unfortunately, prospective data on such changes to family structure were not collected and it is therefore impossible to estimate the number of women whose risk might be changed dramatically as a result.

Extending the family tree through the Registrar General’s records system may enable connections to be made with other already known families and may provide valuable
FIGURE 5a

FIGURE 5b
material for research utilising linkage analysis. This is however a time consuming and expensive exercise.

Methods of Confirmation
The research which has led to the identification of a number of breast cancer susceptibility genes relies on linkage analysis (see Introduction p.20). This in turn is dependent on being able to obtain DNA from as many family members as possible, both affected and unaffected. The most suitable material for this investigation is a blood sample. It is also possible to utilize paraffin embedded pathological specimens from which DNA can be extracted. It is therefore important to be able to identify cases in which the tracing of such material would be possible. In the present series only about 20% of cancers were confirmed by methods permitting the tracing of tissue. In most instances where a pathology laboratory reference number was known, tissue was available when requested, even when the original surgery had been carried out many years previously. In an indeterminate number of cases it may be possible to obtain tissue from other operations unrelated to cancer, such as appendicectomy, which would be equally suitable for genetic analysis. An estimate of the availability of such tissue cannot be derived from these data but the figure is going to be only a proportion of those in which the casenotes can be traced and are available. Casenotes of individuals unaffected by cancer were not routinely requested by us. The proportion available is likely to be similar to that for cancer patients but may be lower, given that many oncology departments preserve notes in perpetuity whereas those for patients with non-malignant conditions are often destroyed after a set number of years.
Impact of Confirmatory Processes

The checking processes to confirm family history are very costly in terms of both labour and resources.

A review of those pedigrees in which inaccuracies had been identified showed that few made a significant difference to the decision on whether or not to screen the proband, although in a larger number the actual level of risk was altered. It is therefore proposed that where only relatively non-invasive management, such as mammographic screening, is anticipated, the family history as given by the proband, or with limited (low cost) confirmatory procedures, can be used for risk assessment. However, if a patient is coming forward for genetic testing or prophylactic mastectomy the pedigree should be thoroughly checked. This is emphasized by the fact that there has been a report of Munchausen’s syndrome presenting with a fabricated family history of cancer (Evans et al., 1997). Three cases have subsequently been encountered in South-East Scotland also.

EVALUATION OF PSYCHOLOGICAL IMPACT

Major concerns in setting up a clinic such as this are that it will attract women who grossly overestimate their risk and who are highly anxious or that risk counselling itself will create unacceptable levels of distress.

Whilst women in this cohort were aware of their increased risk, they were more likely to underestimate it than to overestimate. Variations across studies in the way in which risk estimates are calculated make direct comparisons difficult. In the trial by Lerman et al. (1995), two-thirds of women grossly overestimated their own cancer risk. This may be due in part to cultural differences but women in that trial were
ascertained through a relative currently receiving treatment for breast cancer which may have increased their sense of their own vulnerability. The data presented here more closely echo the experience of the clinic in Manchester (Evans et al., 1993). This sample did have somewhat higher trait anxiety scores than the mean for the general population (Knight et al., 1983) but no higher than for women who elected to attend for routine breast screening (Morris and Greer, 1982). State anxiety scores were no greater than for women attending for routine mammography and were unrelated to the women's baseline risk estimates.

From the point of view of service evaluation, an important finding of this study was that the risk counselling offered did increase the accuracy of the women's perceptions of their own risks. This is in contrast to the findings of Lerman et al. (1995) that the risk estimates of the 2/3 of women who grossly overestimated their risk initially were not modified by counselling. However, although counselling improved accuracy of risk perception in the present study, women still tended to over- or underestimate but to a lesser degree. It is therefore important to attempt to identify the basis of such persistent misperceptions so that they can be addressed.

Mean state anxiety and GHQ scores were significantly lower after counselling than before, confirming what women volunteered at clinic, that they felt reassured by being able to attend. There was no evidence that counselling caused anxiety or distress to those who were made aware that their risk of developing breast cancer was greater than they had previously thought.
RISK ASSESSMENT

A major concern of all familial cancer clinics is that women with a similar family history should be given similar risk estimates and advice regarding appropriate screening and prophylaxis. The "case conference" method employed by the Edinburgh clinic is time consuming and could lead to different assessments given on different days to women with similar family histories. No measures of internal consistency are available for this data set. Moreover, it is important that members of the same family seen in different centres are given the same advice in order to avoid confusion for the patient which could in turn lead to a loss of confidence in the medical profession.

Within Scotland the latter problem is already dealt with fairly efficiently with exchange of pedigrees between the major centres in which familial breast cancer clinics are running (which are all in university teaching hospitals) and good communication about information already given to other family members in a different centre. This system is however very dependent on the patient herself mentioning that a relative has already consulted in a different centre. Nevertheless, no major problems have arisen in this respect over five years.

A computerized system, whereby the family history information is typed in and a program calculates the associated risk would greatly enhance the reproducibility of risk assessments and ensure consistency. Until recently, programs were complex and required to be run on a mainframe computer. The ideal would be a program which could be run on a lap-top computer which would allow calculation of the risk when the woman first attends.
Women's understanding of numerical risks has been shown to be poor both in our own series and that of Evans et al. (1993). What seems to be important to the patient is the recommendation about what to do about that risk in terms of screening, etc. So long as women attending clinics in different centres are given the same advice in this respect, the actual numerical risk given to them is probably of secondary importance. Uniform policies throughout the country therefore need to be agreed and the work of the Cancer Families Study Group has gone at least some way towards addressing these issues. Guidelines are now in place for Scotland and are being adhered to in all centres (Scottish Executive Health Department).

EVALUATION OF PREVIOUS HEALTH-RELATED BEHAVIOURS AND COPING STYLE

Almost 90% of women in this study had previously performed BSE although only 29% did so on a regular basis. Over 50% had previously had mammograms. Figures for both these practices are higher than in the studies by Vogel (1990) and Kash (1992) from clinics in the USA. Differences in the rate of obtaining mammograms may be explained, at least in part, by the fact that individuals in the USA have to fund this investigation privately. No figures are available as to where and when the women in our study had mammograms previously but it is speculated that these will have been done when they attended a symptomatic breast clinic. This is likely to be a valid assumption, given that over 80% of referrals came from this source.

Coping style did not appear to have any effect on health-related behaviours in that monitors and blunters were equally likely to have performed breast examination or obtained mammograms. Thus, even those who adopt a more passive approach to
health care ("blunters") are sufficiently motivated to do what they can about their increased risk –unless they are from the more deprived sector of the population (p. 96). In drawing these conclusions, it is acknowledged that blunters were significantly in the minority amongst the cohort studied.

Given that women who came to the clinic in the first instance did so entirely voluntarily and were asymptomatic, the 16.7% rate of default from the second appointment is quite high. Nevertheless, many defaulters (almost 2/3) had risks below the threshold for mammographic screening and thus only a few women (n=29) missed out because of this. Although women were not told their risk at the first visit some may have picked up indications during the general discussion that the clinician did not think their risk particularly significant and this may be one reason why non-attenders tended to be in the lower risk categories.

EVALUATION OF SERVICE BY GENERAL PRACTITIONERS

The results of the survey among general practitioners generally support the need for a multidisciplinary clinic such as this one where women can receive genetic information, counselling and screening under the same roof without the need to attend several different specialist clinics. The high response rate indeed implies that GPs generally attach great importance to it. It is always possible that there is selection bias in operation in that those who feel most positively about the service may be more likely to return the questionnaire. The response rate of greater than 90% virtually eliminates this as a particularly important factor. The number of non-responders is too small to alter the overall conclusions.
There has been much recent publicity in the press, on television and in women's magazines about the hereditary nature of some breast cancers and the possibility of future genetic testing. With the speed at which advances are made in this field GPs cannot be expected to be in a position to provide genetic counselling. The vast majority therefore welcomed the opportunity to refer such patients to a specialist clinic staffed by personnel with expertise in both genetics and the management of breast disease. It is encouraging that even those who thought the service could be improved would not let this deter them from referring other patients in the future. Some examples of comments received are given below.

"Patients have found it extremely useful."

"I think it is a very important service as women with a family history of breast cancer are increasingly informed of their increased risk and this generates considerable anxiety."

"Breast cancer is a high profile problem. It is also very common and many ladies will have a family history and are therefore keen to be informed as accurately as possible as to their true risk, increased or otherwise, of developing the disease. They are keen to be informed further with regard to prevention, extra screening, etc. The clinic I feel fulfils this role very well."

"Very positive feedback from women who attend. They are reassured and helped."

Most of those who did not think that they would use the service in the future had not done so in the past and seemed to be under the misconception that it was in some way in competition with the services provided by the Edinburgh Breast Unit with which they were already very satisfied. Any future correspondence on the subject therefore needs to address this issue and to emphasize that the genetic counselling
and screening clinic is seen as an integral part of the breast service, has access to the same facilities for assessment and is run by many of the same staff. It is of note that GPs had not previously referred significant numbers of patients directly to the regional genetics service for advice regarding their family history of breast cancer, preferring instead to make use of the specialist breast unit. This would suggest that general practitioners feel that in this situation genetic counselling is better provided by those with specialist knowledge of the specific disease in question. However, as more complex genetic information becomes available and with the development of genetic testing, this attitude is liable to change and the already good links with clinical genetics can only be strengthened.

Not all investigators have had such positive responses. Walter et al. (2001) surveyed general practitioners and their practice nurses about their attitudes to the impact of new genetic services pertaining to breast cancer risk. Many stated that they had “mixed feelings.” The main reasons given for such ambivalence were the increased workload for GPs, a lack of opportunity for education on the subject and a perceived lack of firm guidelines and protocols. Practice nurses tended to have a more positive view than the GPs. It would be interesting to repeat this study in a region such as Scotland where well documented guidelines have been in place for some time (see p. 109).
ETHICAL CONSIDERATIONS

Risk Assessment

Concerns about this aspect have been discussed already (see p. 118).

Issues of Medical Confidentiality

When dealing with issues in genetics, not only the well-being of the individual patient has to be considered. The information given out may have far reaching consequences for other family members as well.

It is obviously important, in the interests of giving as accurate advice as possible to individuals, that family histories are confirmed. However, these checking processes may turn up unsuspected deviations from the reported history which raise questions as to how much should be fed back to the original proband. Perhaps the most delicate of these relate to changes in the family structure.

In the family illustrated in figure 5 (p.114) the proband stated that two first degree relatives i.e. two sisters had been affected by breast cancer premenopausally. This would have given her an estimated lifetime risk of say 40-60%. Confirmation of the pedigree illustrated that she in fact had only two second degree relatives affected i.e. two aunts so that her estimated risk now falls to less than 20%. The proband in this example was actually 50 years old and eligible for screening under the NHSBSP. It can therefore be argued that she need not be told the exact reasons for not including her in special screening. It is not difficult to imagine a situation where such dramatic alterations to the family structure would alter the recommendation given to the proband and knowledge of the changes to what has always been believed by the whole family may have serious psychological consequences.
On occasion, probands from separate branches of a large extended family have attended the clinic quite independently of one another and due to the vigilance of our registry workers and the presence of more unusual surnames within the families, the link has been made. In the past this has provided a number of pedigrees large enough to be studied by linkage analysis where the individual branches of the family taken separately would not have been suitable. It has been our experience (admittedly limited) that in this situation the various family members are only too glad to discover that the making of such a link provides information that could potentially not only help individuals but may also contribute to our overall understanding of genetic susceptibility to breast cancer. However, it is not difficult to envisage situations where knowledge of a link-up with a hitherto unknown branch of the family might be unwelcome.

Further difficulties arise when a patient asks to be given a copy of the family tree. It has been our practice to refuse this request on the grounds that this contains confidential medical information relating to individuals apart from the proband. However, the ruling that patients must be allowed to see their medical records if they request to do so means that such sensitive issues must be handled with extreme care.

Access to Medical Records.

A major change in public attitude to the medical profession and the traditional belief that “doctor knows best” has several implications for genetics clinics.

A move to make it necessary to obtain permission for access to medical records from the patient concerned is likely to hamper the process of attempting to confirm relatives’ diagnoses from this source. Cancer Registry will no longer provide
information on named individuals who are still alive at the time of inquiry so that this avenue is now closed where others have failed to confirm the diagnosis.

A number of high profile cases and the subsequent media outcry regarding the storage of tissue and its use for medical research could have a major deleterious effect on the identification of other breast cancer susceptibility genes (Haites et al., 2001). In many other European countries permission is required from the next of kin for access to pathology specimens and similar attitudes may apply in the UK in the near future.

Pathology specimens from living individuals should only be used with their express permission and, in the event of this being refused, an alternative sample should be sought either from a consenting living relative or from a deceased family member (Nuffield Council on Bioethics guidelines, 1993).

Many of these issues have been considered by the Human Genetics Commission in its report “Inside Information” (2002). The Commission recognises family concerns over the revealing of relatives’ medical history but believes that the individual seeking genetic counselling has the right to disclose it. It is even suggested that holders of information about genetic relatives in a clinical context might be exempted from their normal obligations of notification and provision of information to such relatives under the Data Protection Act.

With respect to the use of genetic material for medical research, the Commission calls for further legislation. Meanwhile, it is advocated that express permission for every single project does not need to be sought where such specimens were donated specifically for research, where general informed consent for their use was obtained at the outset and where specimens have been appropriately anonymised.
Genetic Testing and Insurance

Through the Association of British Insurers (ABI), the insurance industry has applied a voluntary moratorium on the use of genetic tests to influence premiums. It is still permissible to ask for family history information, but in practice most companies ask about only a limited number of medical conditions (cancer among them). This is, for the time being, a voluntary agreement until such times as further consideration can be given to the subject, with resultant legislation if necessary. It is recommended that insurance companies should not be able to demand genetic tests but it is less clear whether they should have access to the results of tests which have already been carried out, and whether they might indeed be willing to reduce premiums for non-carriers in families where a genetic mutation is known to exist.

Preventative Strategies

If the proband is considering genetic testing or prophylactic mastectomy then risk may have to be explained in more detail, revealing information about relatives and family structure of which she was formerly unaware and which moreover are confidential to the other family members involved. The availability of genetic mutation analysis could simplify such dilemmas in that all that would then be required would be to identify the mutation responsible for breast cancer susceptibility in that particular family (using DNA from a single affected individual who is willing to participate) and offer the test to unaffected individuals regardless of their relationship to the affected mutation carriers. However, the growing number of disease causing mutations now identified in the major breast cancer susceptibility genes means that this process is often not nearly so simple as it may sound.
Individuals from such families will continue to pose difficult ethical problems for geneticists. Regulations are also continually changing, being overseen by the Human Genetics Commission but also influenced by patient representative groups.

LESSONS LEARNED and their IMPLEMENTATION

This observational study refers to the period 1992-1995. Our experience has shown that there is a sustained demand for genetic counselling and screening services for those with a family history of breast cancer. Women are often ill-informed about what the actual risk is although virtually all perceive that it is increased. It is evident from the survey of general practitioners reported here that most of them also feel unable to provide appropriate reassurance or advice on cancer risks and screening either due to lack of knowledge or short consultation times. This group therefore also welcomes the provision of an integrated service for their patients.

The provision of a specialist service which also incorporates a screening facility is, however, costly in terms of both time and resources. As increasing numbers of patients require to be seen for regular follow-up as well as accommodating a steady number of new referrals, waiting times for a new-patient appointment inevitably increase unless there is a parallel increase in resources. In an ever more stretched health service with demands on resources from many sectors, funding is already difficult to secure.

Ways whereby the efficiency of the service can be improved without necessarily increasing costs therefore need to be found. One possibility, which is employed in other health regions, would be to provide a centralised genetics service with screening activity devolved to local breast clinics. This has some advantages in that
discussion on the genetic aspects of a disease can be broadened to include other genetically linked diseases such as colon and ovarian cancer. The patterns of cancer family syndromes such as Li-Fraumeni or Lynch type II may be more readily recognised in this setting. There are also many disadvantages to this approach. Firstly, screening recommendations made by the geneticist may not be carried out by local clinics who themselves have no additional funding for the screening of young (under 50) asymptomatic women. The efficacy of breast screening by mammography in this group is as yet unproven. Only by having a centralised service which is subject to the same quality control measures as the National Breast Screening Programme can this issue be adequately addressed. In this way data from many larger clinics can be pooled to provide sufficient numbers to answer the question of efficacy. Not least, it is costly to the women themselves in time, effort and monetary terms to make separate visits to genetics clinic and screening centre which for many regions may in fact be many miles apart. In this situation, the unequal access of women from social classes I and II (compared with those from social classes IV and V) to preventative services which is already evident from this study can only deteriorate.

Some authorities believe in the separation of genetic and breast care services (Ponder, 1994). Trials are extremely difficult to organize and monitor in such settings.

Multidisciplinary clinics such as this one offer a comprehensive service in a single centre. The inclusion of a cancer geneticist in the team allows for the recognition of cancer family syndromes, such as the Lynch type 2 families, and risk of cancer at sites other than breast. Appropriate referral to those with expertise in screening for
these conditions can then be made. Locally there are good liaisons with the gynaecologists who provide ovarian screening and general surgeons who are responsible for colonoscopic surveillance.

A combined approach is probably most important at the first visit when basic genetic counselling is undertaken. Much of the information imparted at this consultation is however very repetitive and applicable to all families. To this end a video has been prepared for use locally to outline some of the more general aspects of heredity and genetics. A second video addresses issues specific to familial breast cancer. Patients are asked to view the video before seeing a doctor. This means that there is more time available for discussion of issues relating specifically to the individual and her family (Cull et al., 1998).

At the time of the study reported in this thesis it was our practice for clinic staff to record systematically the family history taken from the patient. Verification then took place prior to the second clinic visit (a period of approximately 3 months) when the risk assessment was communicated to the patient. Currently, a standardised family history questionnaire is mailed to patients for return and verification prior to any clinic appointments being sent out. Screening, where considered appropriate, is now carried out at this same appointment. Patients who are considered not to be at significantly increased risk are informed by letter and are not invited to the clinic. The decision is also communicated in writing to the patient’s GP.

Associates in cancer genetics are now being employed to provide a link between the specialist clinic and community based healthcare services. Their role is to help with the verification of the family histories, provide a back-up to the GPs for those women
not at increased risk who are discharged, and to form a route for re-referral should there be any new developments in the family history.

It is important to maintain a specialist input from those with expertise in the diagnosis and treatment of breast cancer for a number of reasons. Patients often have questions about their relatives’ treatment. Whilst it should never be the primary role of the genetics clinic to provide a forum for this type of discussion, reassurance can often be given in the course of the consultation. Mammographic screening alone is unproven in this situation although initial results are promising in that detection rates appear to equate with those from the NHSBSP. Women often lack confidence in examining their own breasts and an ideal opportunity to educate them arises in such a multidisciplinary service. In addition, the pros and cons of prophylactic mastectomy and alternative methods of reconstruction must be discussed with the patient by a specialist breast surgeon with experience in all the available techniques. In addition, many women will have questions about use of the oral contraceptive pill, hormone replacement and, increasingly, alternative therapies. Finally, it is desirable that there should be regular input from a geneticist to update patients and fellow staff on developments in this rapidly expanding area. In turn, geneticists themselves welcome the opportunity to keep abreast of developments in the treatment of breast cancer, such as new chemo/endocrine regimes and monoclonal antibody therapy.

The cost effectiveness of any screening programme is, by its very nature, increased by being able to define more accurately the appropriate level of risk at which to offer screening, a variable which may alter in the light of experience. For example, guidelines may be revised to recommend screening if a single first degree relative is
affected under the age of 35, rather than 40 years as at present. Numbers of unaffected female relatives might be factored in to the equation.

As knowledge about mechanisms of action of the various predisposing gene mutations accumulates, management of the individual is likely to become more tailored to the category of risk. For example, there is now good evidence that prophylactic oophorectomy not only dramatically decreases the risk of ovarian cancer but also reduces the risk of breast cancer by about 50% in carriers of BRCA1 and 2 mutations, a benefit which does not appear to be negated by the subsequent use of hormone replacement therapy (Rebbeck et al., 2002). Generally speaking, such surgery should not be offered to women without BRCA1 or 2 mutations as there is no evidence to support its efficacy in other types of genetic breast cancers. (Kauff et al., 2002; Rebbeck et al., 2002). It may, however, be offered where there is a strong suspicion of a BRCA1 or 2 mutation based on the pattern of cancers in the family. In a proportion of these families mutation testing will take a long time, especially if the mutation is one of the less common ones, and some women may not be prepared to wait.

With regard to chemoprevention, most studies have shown that the benefit from tamoxifen is applicable to oestrogen receptor (ER) positive cancers and that there is little or no reduction in the incidence of ER negative tumours. BRCA1 tumours are more frequently ER negative and thus chemoprevention with tamoxifen is unlikely to be effective in these families (the same does not apply to BRCA2 tumours). The most recent data from the IBIS (International Breast Intervention Study, 2002) trial show a 32% risk reduction with a median follow-up of 50 months. Age, degree of risk and use of HRT did not affect the risk reduction.
A major element missing from cost-effectiveness analysis is quality of life. Some work has been done with regard to prophylactic surgery, but not with respect to long-term screening, chemoprevention, genetic testing or simply living with the knowledge of increased risk. This remains an area for further research, especially as quality of life issues may actually change with evolving genetic technology.
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APPENDIX 1.

Text of Information Letter Circulated to General Practitioners

Breast cancer is the commonest cause of death in women aged 35-54. Although mammographic screening is effective in reducing the mortality from breast cancer in women over the age of 50, the benefit in younger women is less well defined. By identifying a specific population of young women at high risk of breast cancer it may be possible to concentrate on the benefits of screening. Predominant risk factors in premenopausal women include genetic predisposition and atypical epithelial hyperplasia on previous breast biopsy.

A genetic predisposition is thought to account for at least 5% of all cases of breast cancer but a much higher proportion of cancers diagnosed before the age of 50. The empiric lifetime risk of a woman developing breast cancer is increased threefold (to 1 in 4) over that of the general population (1 in 12) when a first degree relative has been affected before the age of 50 years. In addition, defined families have been identified in whom the inheritance of breast cancer exhibits Mendelian dominant characteristics. Women who have had a previous breast biopsy showing severely atypical epithelial hyperplasia are 5.3 times more likely to develop breast cancer than women with non-proliferative lesions. Women with both a family history and atypical hyperplasia are at 11 times increased risk.

Many women are now aware of this familial risk through publicity in the popular media and there is a growing demand for screening, risk assessment and counselling. Recent advances in molecular genetics also make it possible to define risks more accurately in a proportion of cases and these techniques are rapidly evolving. In
response to this perceived demand we are offering a co-ordinated genetics/cancer screening clinic to young (i.e less than 50 years) women at high risk. The clinic is based at the South-East of Scotland Breast Screening Centre but is run in collaboration with the MRC Human Genetics Unit at the Western General Hospital and the University of Edinburgh departments of surgery and pathology. It is vital to evaluate this service thoroughly since at present it is funded largely from research grants. We shall therefore ask all women who have been referred to participate in careful documentation, not only of their family tree, but also of their own anxiety levels and manner of coping with their cancer risk status.
APPENDIX 2.

CONSENT FORM

I am willing to take part in the study of breast diseases in families. I have read the information letter and understand the purpose of the study.

I consent to information relating to my family history of breast and other diseases being stored as part of the study and that, if necessary, medical records may be obtained to confirm this information. I understand that all such information will be kept strictly confidential and will not be released in any form in which I or my family members can be identified.

I also give my permission for the withdrawal of a single 20ml blood sample from myself which I understand will be stored and used for research purposes both now and in the future.

Signed.................................................. Date....................................................

Name.................................................. -
(BLOCK CAPITALS)
Date of birth............. Home telephone no..........................

Address..................................................
...........................................................
...........................................................

Name and address of family doctor (GP)
...........................................................
...........................................................
...........................................................

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APPENDIX 3.

1. Do you practice breast self examination regularly?

Never/occasionally/every few months/ every month/ more than once a month/more than once a week.

2. In the last 3 years, how often on average have you attended any of these clinics for breast examination?

<table>
<thead>
<tr>
<th>Clinic Type</th>
<th>never year</th>
<th>less than 1 per year</th>
<th>about 1 per year</th>
<th>2-3 per year</th>
<th>more than every 2 mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>well woman clinic</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital based clinic</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>private clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Do you feel able to adequately assess your own breasts?

Y/N

If not, why not?

4. Have you ever had any professional teaching as to how to examine your own breasts properly?

Y/N

5. Do you want to be shown how to examine your breasts properly?

Y/N

6. Are you reassured by doctor/hospital visits?

Y/N
7. Do you think having more information about breast cancer risk would make you feel more anxious? Yes/No/Not sure/Don’t know.

8. Do you think this would diminish anxiety? Y/N

9. Do you worry about developing breast cancer

   Every day/week/month/year/never/occasionally
APPENDIX 4.
We are interested in women’s attitudes to breast care.
Please mark the answers to the following questions which are closest to your own situation. Please answer all the questions.

1. Do you examine your breasts:
   Never
   Occasionally
   Every few months
   Every month
   More than once a week
   Most days

2. Do you feel able to adequately assess your own breasts?
   Yes
   No

3a. Have you been shown how to examine your breasts properly?
   Yes
   No

3b. If no to 3a, do you want to be shown how to examine your breasts properly?
   Yes
   No

4. If you found a lump while you were examining your breasts what would you do?
   Put off going to see a doctor
   Wait a few days to see if it would go away, then see a doctor
   Try to see a doctor straight away
   Other, please specify

5. In the past year, how often on average have you attended any of these clinics for breast examination

<table>
<thead>
<tr>
<th></th>
<th>never</th>
<th>about once</th>
<th>2 or 3 times</th>
<th>more than every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Well Woman Clinic</td>
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</tr>
<tr>
<td>Hospital Clinic</td>
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<tr>
<td>Private Clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Are you reassured by having your doctor examine your breasts?  Yes/No

7. Have you had a mammogram in the last year?  Yes/No
8. How much do the following apply to you?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am afraid to examine my breasts in case I find a lump</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is difficult to take time off work or other commitments to go to clinics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is difficult/expensive to travel to clinics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I find it embarrassing to have my breasts examined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am afraid of having my breasts examined in case the doctor finds a lump</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I find having a mammogram uncomfortable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am worried about being exposed to radiation through being screened too often</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being referred to a genetic risk clinic has made me worry more about breast cancer</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
9. Please mark the appropriate box to indicate how much you agree/disagree with the following opinions.

<table>
<thead>
<tr>
<th>Strongly agree</th>
<th>Agree a little</th>
<th>Disagree a little</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>If more women went for breast screening there would be fewer deaths from breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My health is too good at present even to consider that I might get breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If a lump is found in your breast it is usually too late to do anything about it</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whenever I hear of a friend/relative or public figure with breast cancer I realize that I could get it too</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If I examine my own breasts regularly I might find a lump sooner than if I go for screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There are so many things that could happen to me that it is pointless to think about breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A woman can have breast cancer without any symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The older I get the more I think about the possibility of getting breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammography can reveal small breast cancers before they can be felt</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I am worried about the risks of breast cancer for my children</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10. People differ in how health conscious they are these days. In your everyday life how important are the following to you:
Note: some things like stopping smoking may not apply to you. Where an item does not apply please mark the N/A column.

<table>
<thead>
<tr>
<th></th>
<th>not at all</th>
<th>a little</th>
<th>quite a bit</th>
<th>very</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losing weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A low fat diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A high fibre diet</td>
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<td></td>
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</tr>
<tr>
<td>Reducing stress</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Taking exercise</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Stopping smoking</td>
<td></td>
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<tr>
<td>Drinking only a moderate amount of alcohol</td>
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<tr>
<td>Other</td>
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</tbody>
</table>

11a. Have you done anything else to safeguard your health in the past year?
Had a cervical smear Yes/No
Had any other sort of screening or health check ---- please specify

11b. Are you currently taking:
Oral contraceptive pill Yes/No
Hormone replacement therapy Yes/No

If yes to either of these please indicate how long you have been taking it.

12a. Have you been suffering from menopausal symptoms in the past 3 months? Yes/No

12b. If yes, have you discussed hormone replacement therapy (HRT) with a doctor? Yes/No

13. Which of the following is closest to your view of the situation with regard to HRT?
I can safely have HRT for as long as is necessary to relieve menopausal symptoms
I can safely have HRT for a short time to relieve severe menopausal symptoms
I should avoid having HRT and find other ways to cope with menopausal symptoms
I do not know whether I can safely have HRT
14. People differ in their views about genetic risk and what approaches they would find acceptable to reduce that risk. Please indicate your reaction to the following statements:

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>If genetic testing were available I would want to know for sure whether or not I had a cancer gene</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I would prefer to have regular screening and do nothing else unless cancer develops</td>
<td></td>
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</tr>
<tr>
<td>I would be willing to take drugs on a daily basis to see if that would reduce the risk of getting cancer</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I would be willing to have surgery to remove my breasts to avoid getting breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I would prefer not to have regular screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15a. At this moment, how susceptible do you feel you are to developing breast cancer?  
very  
moderately  
not very  
not at all

15b. How confident are you that attending the family risk clinic is of benefit to you?  
very  
moderately  
not very  
not at all
APPENDIX 5.

Clinic for Genetic counselling and Screening of Women with a Family History of Breast Cancer

1. Were you aware of the existence of this clinic? Yes/No

2. Where did you hear of the clinic? (Tick as many as apply):
   a. information letter from clinic [ ]
   b. verbally from other patients/relatives [ ]
   c. GP study day [ ]
   d. other, please specify [ ]

3. Have you referred any patients to this clinic?
   Yes/No
   If yes, approximately how many?
   1-5
   6-10
   11-15
   >15

4. Were you satisfied with the service they received?
   Yes/No
   If no, please specify areas of dissatisfaction

5. Would you refer other patients to this clinic in the future?
   Yes/No
   If no, why not?
APPENDIX 6.

INFORMATION FOR FAMILIAL BREAST CANCER PATIENTS.

This information sheet is intended as a written reminder of some of the points covered in your discussion at the clinic. If there are any areas which remain unclear or any topics you wish to discuss further, then please do not hesitate to get back in touch.

SCREENING

You have now been enrolled in a research programme which has been funded for 3 years to evaluate the need for and effectiveness of counselling and screening for breast cancer in young women who have relatives affected with this disease. This screening takes the form of breast x-rays (mammograms) together with breast examination. Mammography aims to pick up early and small breast cancers at a stage when treatment is likely to be easier and more effective. (At this early stage it may not be possible for either you or a doctor to feel a lump). Screening does not prevent breast cancer. A small proportion of cancers do not show up well on x-rays and may therefore be missed.

BREAST EXAMINATION

You are encouraged to examine your own breasts on a regular monthly basis. We appreciate that some women may feel unable to do this for various reasons. Leaflets entitled "Being Breast Aware" are available in the clinic. If you have any further queries please do not hesitate to ask.
CONFIDENTIALITY

On your first visit to this clinic you gave permission for personal information on family history to be stored on file. All such information is confidential and will not be released to any other members of your family without your permission. It may however be combined with similar information from other clinics operating along the same lines as this one in different parts of the country, for research purposes. It may also be desirable for us to contact other members of your family but we would not do so without your express permission. Naturally we would not contact anyone whom you think might be upset by such an approach.

LIFESTYLE

1. Diet

A high fibre, low animal fat diet may reduce the risk of both breast and bowel cancer. There is also some evidence that vitamins A and C (found in fresh fruit and nuts) are protective.

2. Hormone Replacement Therapy

The relationship between HRT use and breast cancer is uncertain. We therefore advise that HRT may be taken in low doses and for as short a time as necessary to control menopausal symptoms.

3. The Pill

Again, the relationship between use of the oral contraceptive pill and breast cancer risk is uncertain. If this is relevant to you please ask to discuss the subject further in the clinic.

4. Stress
There is no medical evidence to prove that stress causes cancer. It is true, however, that stress reduces the ability to cope with difficulties. It is therefore beneficial to general health and well-being to have a number of strategies for coping with stress (relaxation, leisure activities, etc.)

**DRUG TREATMENT**

Some breast cancer cells need the female hormone oestrogen to grow. Tamoxifen is a drug widely used to treat breast cancer by preventing the cells getting oestrogen.

An international study is taking place to determine whether Tamoxifen can help to protect women at higher risk of breast cancer. Half of the women who take part in the study will be given Tamoxifen and half an inactive tablet to take daily for 5 years. While the trial is in progress neither the woman nor her doctor will know which form she is taking.

If you are interested in taking part please ask us for further information.

**GENETIC TESTING**

It may be possible in the future to offer direct genetic testing (by a blood test) to find out if someone has actually inherited an altered gene which increases her risk of developing breast cancer.

We will only be able to test you if the particular altered gene causing breast cancer in your family has been identified. This will be done by examining a sample from a member of your family who has had breast cancer. If an altered gene is detectable in them, testing should become possible for other family members.

Until all gene faults which can cause breast cancer have been identified, testing will
not be possible for everyone who would like it.

The pre-testing procedure involves counselling sessions to ensure that all the potential consequences of testing have been considered.

It is advisable that insurance policies and mortgages are taken out if required before embarking on testing in case the result has an adverse effect on premiums.

It should be remembered that breast cancer is a common disease in the population as a whole. A negative test for an altered gene does not eliminate that "background" risk which applies to all women.
PUBLICATIONS AND PRESENTATIONS


Whilst not directly related to the evaluation of the clinical service, contributions were made to the following publications, based on material gathered during the confirmation of family histories:


The following presentations have been made, based on the work contained in this thesis:

September 1993  
Experience with a familial breast cancer screening clinic. 
Nottingham/EORTC joint breast meeting, Nottingham.

December 1994  
Referral criteria for familial breast cancer clinics: Can we do better? 
UK Cancer Families Study Group meeting, London.

November 1995  
Accuracy of family history reported by patients attending a familial breast cancer screening clinic. 
EU Concerted Action on Hereditary Breast Cancer meeting, Heidelberg, Germany.

September 1998  
General practitioner attitudes to familial breast cancer counselling and screening services. 
EU Concerted Action on Hereditary Breast Cancer meeting, Dublin.
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