# Familial breast cancer: some social, economic and ethical issues

C. MICHAEL STEEL, M.D.[1], PATRICK J. MORRISON, M.D.[2], PÅL MØLLER, M.D.[3], D. GARETH EVANS, M.D.[4], NEVA E. HAITES, M.D.[5], HANS VASEN, M.D.[6], SHIRLEY HODGSON, M.D.[7], DIANA M. ECCLES, M.D.[8], DOMINIQUE STOPPA-LYONNET, M.D.[9], JENNY CHANG-CLAUDE, M.D.[10], GENEROSO BEVILACQUA, M.D.[11]

*School of Biological and Medical Sciences[1], University of St Andrews, Regional Genetics Centre[2], Belfast City Hospital, Belfast, Unit of Medical Genetics[3], The Norwegian Radium Hospital, Oslo, Regional Genetic Centre[4], Department of Medical Genetics, St Mary's Hospital, Manchester, Department of Medical Genetics[5], University of Aberdeen, Aberdeen Medical school, Aberdeen, Netherlands Foundation for the Detection of Hereditary Tumours[6], Academisch Ziekenhuis Leiden, Leiden, Division of Medical and Molecular Genetics[7], Guy's Hospital, London, Wessex Regional Genetics Service[8], Level G Princess Anne hospital, Southampton, Unité de Génétique Oncologique[9], Institut Curie, Paris, Division of Endocrinology[10], Arbeitsgruppe Genetische Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Institute of Pathology[11], University of Pisa, Pisa*

**ABSTRACT** Demand for clinical services for breast cancer families has grown enormously in recent years. Much attention has focused on high penetrance "breast cancer gene" mutations but these are rare and, overall, a more substantial contribution to the genetic component in breast cancer etiology comes, almost certainly, from common low penetrance mutations or polymorphisms in genes that have yet to be identified. In offering services for breast cancer families, there should be open acknowledgement of the high degree of uncertainty surrounding current practice – risk evaluation for any individual family member, the role of environmental factors interacting with genetic predisposition and the value of any particular screening or intervention protocol. Nevertheless, evidence is accruing that most women derive psychological benefit from enrolment in a familial cancer programme and that regular clinical/mammographic screening for those at increased risk is effective in detecting very early-stage tumours, even in young women. It is essential that prospective audit of the outcome of such programmes continues, including careful measure of their cost-effectiveness. Advances in molecular technology, leading to an increased rate of detection of causal mutations among breast cancer families will help to concentrate resources on those at highest risk but will highlight important ethical questions relating to confidentiality, duty of care and possible discrimination against mutations-carriers. If the effects of clinical and laboratory services for cancer families are shown clearly to be beneficial, it is likely that some of these ethical issues will become less contentious.

*Key words* breast cancer families, clinical services, risk assessment, ethics, economics

*Address correspondence to:*

**Michael Steel, M.D.**
School of Biological and Medical Sciences
Bute Medical Building
St. Andrews, FIFE, KY16 9TS, Scotland, U.K.
Phone (44 1334) 463 558 Fax (44 1334) 463 482
E-mail cms4@st-and.ac.uk

**BACKGROUND** The more we look for familial breast cancer, the more we find it. Nevertheless, specific clinical provision in terms of counselling, risk assessment, screening and molecular genetic diagnostic services for women who believe themselves to be at increased risk of the disease is still rudimentary, at best, in most countries (1-2). Many affected families have long suspected that genetic factors can play a major part in breast cancer susceptibility and clear evidence to support this view has accumulated in the medical literature over the past century and a half (3-4). Yet it was only with the development of techniques for identification of disease genes (i.e. within the past two decades) that the issue of hereditary predisposition to common cancers entered the realm of widespread public concern. Now the popular media regularly carry features about families affected by breast or other cancers and the demand for appropriate services has grown explosively.

**EPIDEMIOLOGY AND THE SPECIFICATION OF RISK** Very few families present such incontrovertible evidence of the heritability of breast cancer as that reported by *Paul Broca* (3) *(Figure 1)*. Much more commonly, we find an apparent excess of affected close relatives of breast cancer patients, particularly when the disease has presented at an early age. Systematic studies of consecutive series of patients yield a positive family history in some five percent of cases (5). However there are caveats. First, the taking of family histories is notoriously error-prone, even when considerable effort is applied. In a twin study, where one twin had breast cancer, the affected twin reported fifty percent more relatives with breast cancer than her unaffected sister (6). Second, the definition of what constitutes a

*Table 1.* Epidemiological approaches to hereditary element in breast cancer

| |
|---|
| Segregation analysis in collections of multi-case families: e.g. from Denmark and the USA (7-9) |
| Studies based on national registries or geographically defined populations e.g. from Iceland or the UK (10-11) |
| Case-control analysis of 5000 cases diagnosed under the age of 55 from the Cancer and Steroid Hormone ("CASH") study in the US (12) |
| Prospective study by interview/questionnaire of registered nurses in the US (13) |

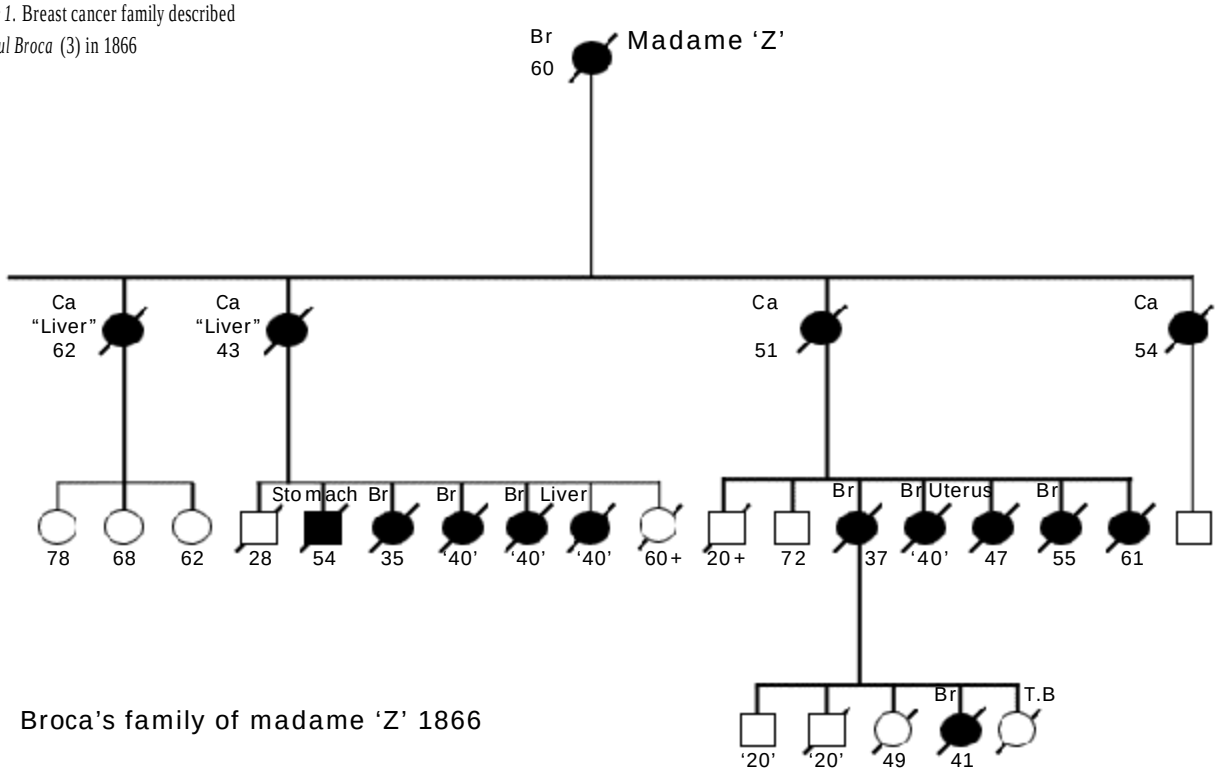
*Table 2.* Empirical relative risks of breast cancer, according to family history

| Affected relatives | Relative risk |
|---|---|
| 1 first degree <45 | 2.2-3.8 |
| 1 first degree >45 | 1.4-1.6 |
| 1 first degree, bilateral | ~5 |
| 2 or more first degree | 2.5-8 |
| 2 or more second degree | 1.5 |
| 1 or more first degree with ovarian cancer | 1.3-1.9 |
| 1 male first degree | 2.3 (female) 6.1 (male) |

positive family history is somewhat arbitrary. The figure of five percent may therefore be an under- or an over-estimate. Third, in very many multi-case breast cancer families the pattern of inheritance of a putative susceptibility gene is not consistent with simple Mendelian concepts *(Figures 2a and 2b)*, requiring allowance for unaffected carriers (female as well as male). Fourth, because breast cancer is a relatively common disease, affecting up to ten percent of the female population of developed western countries, it is inevitable that many extensive families will include one or more sporadic cases which may be indistinguishable from those attributable to a genetic predisposition. Finally, the families that have proved of greatest value for defining the genetic basis of familial breast cancer and for locating the relevant genes are, by definition, unusual. They are large, well documented, accessible, and include substantial numbers of affected individuals. It is important to remember that data, particularly numerical data, derived from them may not extrapolate directly to the more typical families that constitute the bulk of cancer genetics practice.

Despite these caveats, the effort that has gone into many large scale studies of the genetic epidemiology of breast cancer has been richly rewarded and more recent molecular findings have upheld their principal conclusions. The original epidemiological surveys were of four main types *(Table 1)*. They drew on collections of multi-case families, on National registration data, on case-control cohorts of women whose health records were scrutinised in relation to the use of steroid hormones (mainly the contraceptive "pill") and on a massive volunteer cohort of American nurses. This last study is the only one with an exclusively prospective design but it records family history data for the maternal lineage only and thus can pro-

*Figure 1.* Breast cancer family described by *Paul Broca* (3) in 1866



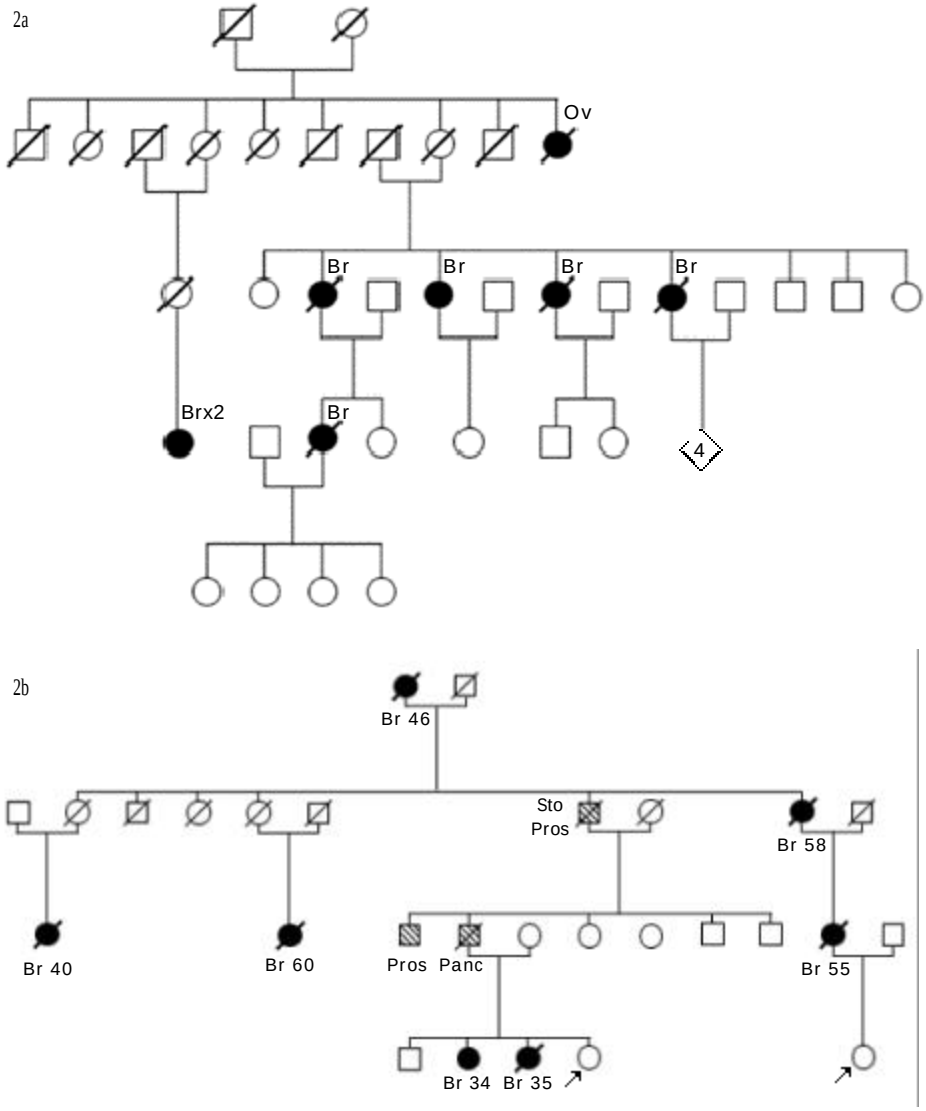
vide no estimates of possible breast cancer risk inherited via the father.

The wide variety of epidemiological approaches has led to a surprising uniformity of conclusions. It is inescapable that a significant minority of breast cancers result from heritable factors behaving as autosomal Mendelian traits, most probably with dominant expression and high, but limited, penetrance. These tumours are characterised by early onset (often under age 50) and, in many families, there is also a high incidence of other cancers, notably ovarian but, at least in some series, also including prostate, large bowel and uterine. From the raw data, empirical risks for women with particular types of family history have been calculated *(Table 2)*.

What is precise to the statistician and the epidemiologist, however, may not translate into a straightforward message for an individual family or an individual woman presenting for risk assessment and counselling at a "family history clinic". One of the hardest tasks of the counsellor – whether he/she is a geneticist, breast surgeon, general practitioner or some other health care professional – is to explain the degree of uncertainty that accompanies translation from the general to the particular. There have been several useful studies of risk perception and associated distress levels among women attending breast cancer family clinics (17-24). Experience in all the clinics participating in the Demonstration Programme confirms that considerable time must be allocated to dealing with these issues that may need to be revisited repeatedly during the years of follow-up surveillance.

Rapid advances in the molecular genetics of familial breast cancer are leading to much more precise risk estimates for a growing proportion of multi-case families but in most centres, at least for the immediate future, the majority of those seeking advice cannot be offered predictive molecular testing. Even when this option is available, uncertainties remain about the advantages and disadvantages of proceeding with the test, about the age-specific cancer risk associated with any given germline mutation and the environmental or genetic factors that may influence the development of breast, ovarian, or other cancers. These uncertainties underlie most

*Figure 2.* Two representative breast cancer families seen in South East Scotland clinics. **a** Note one incidence of ovarian cancer (Ov) and at least three unaffected obligate carriers of the cancer gene mutation in generation two, the mother of four unaffected sisters and the grandmother of the individual with bilateral breast cancer (Brx2), in generation three, the mother of the bilateral case. **b** Note that this family was identified through two separate probands (arrowed) who did not know of their common ancestry. There is at least one obligate carrier of the predisposing mutation in generation two, the mother of the individual affected at age 40. The patient in generation three diagnosed at age 60 may have been a sporadic case, hence the carrier status of her mother is uncertain. There has been transmission of the trait through two males, one of whom (generation two) had both stomach and prostate cancer. The other (generation three) had pancreatic cancer. He had a brother with prostate cancer whose carrier status is unknown.



of the social, economic and ethical issues that need to be addressed.

The teasing apart of social, economic and ethical problems is, admittedly, an artificial exercise and indeed they are closely interwoven with technical developments – the changing "art of the possible" – nevertheless, for the sake of clarity a number of specific issues will be examined under distinct headings.

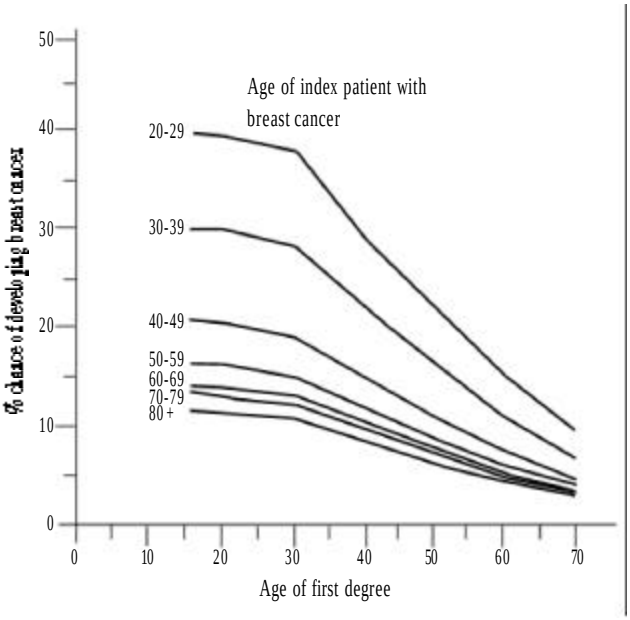
**HOW CAN WE ASSESS RISK FOR AN INDIVIDUAL FAMILY MEMBER?** There are three questions to be addressed in making the calculation: 1. What is the chance that there is a mutant gene in this family predisposing to breast cancer? 2. What is the chance that this particular family member carries that mutation? 3. What is the risk (lifetime, or over a given period) of breast cancer for a carrier of that mutation?

In general, the first two questions pose little difficulty. Where there are multiple affected relatives, particularly if they have been affected at an early age, it becomes virtually certain that a mutant gene is responsible. For smaller kindred, age at onset and closeness of relationship between the affected individuals are important considerations and charts of the type shown in *Figure 3* are helpful in calculating the probability of an underlying genetic explanation for the observed pattern. The position of the individual family member in the family tree allows a straightforward calculation of the prior probability of being a mutation carrier but an adjustment then must be made for current age, based on the concept of residual risk that diminishes with time. A woman of seventy-five who is free of any cancer is considered unlikely to be carrying a mutant breast cancer gene, even if she has many affected first degree female relatives. This revision of the prior probability is particularly important in estimating risks to the daughters of that woman and the principle obviously applies also in reverse. Thus if, within a multi-case family, a potential mutation carrier died very young from unrelated causes, she cannot be classified as unaffected for the purposes of calculating her daughters risks.

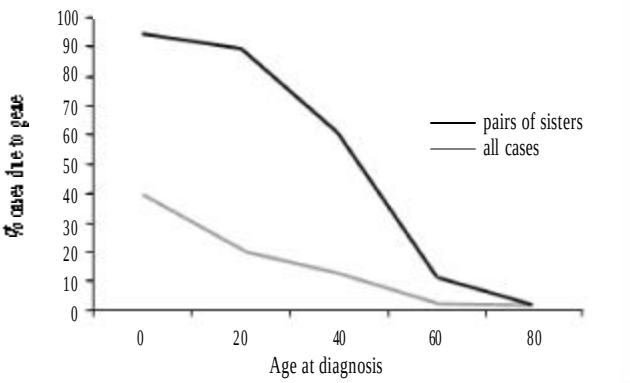
The diminution with time in risk of being a carrier depends on the estimate of penetrance of the cancer trait and views on that subject are undergoing continuous revision. While this has a measurable effect on our calculation of the answer to question 2., it is crucial to question 3. Furthermore, there is the issue of what determines penetrance. If this is entirely a matter of chance, then by accumulating data on large numbers of families, we should be able to arrive at a reliable mean figure. There is, however, at least the suspicion that for BRCA1, BRCA2, ATM and p53, the precise nature and position of the mutation may affect both penetrance and the pattern of cancers in carriers (27-30). Whether these findings should influence advice given to carriers of known mutations is still a matter of controversy and, in any event, for most women currently attending breast cancer family clinics, no mutation has yet been identified in their family. The past history of their own family therefore remains the best basis for an individualised estimate of penetrance. This practice is supported by data from Icelandic families who carry the same BRCA2 mutation but who show significant inter-family differences in cancer pattern, implying perhaps the operation of unidentified modifying genes (31).

Past history, however, may not be an adequate guide to future events. Another controversial area is the interaction of genetic

*Figure 3.* Charts to assist individual breast cancer risk assessment. **a** Lifetime risk for women with one first-degree relative affected at a given age: note that the residual lifetime risk for the unaffected relative declines with advancing age (25). **b** Proportion of cases due to a single gene: the lower curve refers to single cases of breast cancer presenting at different ages while the upper curve refers to pairs of affected sisters presenting at different mean ages (26).




Proportion of breast cancer attributable to a single predisposing gene, according to age at diagnosis and whether or not there is another affected first-degree relative



and environmental factors in breast cancer risk. In a number of families for which data are available over several generations, the age of onset of cancer seems to be declining and its frequency increasing (32-33). It is difficult to know to what extent this apparent trend can be explained by selection bias. If it is real, can it be attributed to the same environmental factors that seem to account for the rising incidence of breast cancer in most western populations? This, of course, is an important question not only in the context of risk assessment but, more importantly, in relation to the advice that may be given to family members about measures that they can take to minimise their own risk. At present the evidence is simply insufficient to be certain whether reproductive history, breastfeeding, use of oral contraceptives or HRT, diet, alcohol consumption or any other component of "lifestyle" materially influences the cancer risk for carriers of breast cancer gene mutations (34-35). Data from North America do seem to indicate that where there is a family history of breast and ovarian cancer, risk of the latter is substantially reduced among users of oral contraceptives though whether this is accompanied by an increase in risk of beast cancer remains uncertain (36-37). A similar study suggests that for carriers of BRCA1 mutations, childbearing may actually increase, rather than reduce, the risk of breast cancer (38).

**WHAT IS THE VALUE OF ANY INTERVENTION IN THE MANAGEMENT OF BREAST CANCER FAMILIES?** At one extreme, the view is sometimes expressed that providing a service for breast cancer families does more harm than good since it simply draws attention to a problem for which there is no solution and hence adds to pre-existing anxiety. Aside from the observation that the demand for such services comes from the families themselves, that attitude can be countered by direct measurement of the effects of cancer family clinics, showing that psychological distress is reduced rather than increased by attendance (24, 39-40). However, most clinicians involved in this field would hope to offer something more than a sympathetic ear and an explanation of the principles of genetics. The management most commonly deployed is screening and evidence is accruing from several centres that a combination of regular clinical examination by an experienced professional and high quality mammography does result in detection of "early" breast cancers which carry good prognostic indicators (41-45). This Demonstration Programme has contributed substantially to the gathering and collation of this kind of information (46). Follow-up data, though still limited, appear to confirm the expectation of a good outcome from conventional surgical management of screen-detected tumours (44-46).

Most centres offer annual screening to women judged to be at 20% lifetime risk of breast cancer (or around 2.5 times the population risk), starting at age 35 or five years earlier than the age at diagnosis of the youngest affected relative. Mammography may be confined to alternate years until age 40 because of concerns about radiation exposure and in some clinics only the first (baseline) mammogram requires two views, subsequent examinations depending on a single oblique film of each breast. In both respects, however, practices vary and only prolonged follow-up will determine the optimal policy. Tumour detection rates appear to range from 4 to 8 per thousand examinations, which is comparable to the outcome of large-scale mammographic screening programmes for unselected women over 50 years of age (47). The findings suggest, however, that mammography alone (i.e. without expert clinical examination) would miss a substantial proportion of tumours in these younger women (44-46).

The question of when to stop intensive screening is a difficult one. In many breast cancer families there are examples of women who were diagnosed in their fifties or even later and this is entirely consistent with new data on lifetime penetrance of BRCA1 and 2 mutations. If a woman is known to be a mutation carrier, few clinicians would be happy to stop specific screening at age 50 (transferring her to a routine national breast screening programme if that exists). If her mutation status is unknown, the choice is less clear and, pragmatically, the policy adopted may depend on the number of older onset cases previously recorded in her family. A compromise that is available in many centres in the UK is to arrange an extra mammogram midway between the three yearly examinations offered under the National breast screening programme, from age fifty, and to carry out physical examination at the same eighteen month intervals.

Magnetic resonance imaging as an alternative to mammography is currently too expensive and too labour intensive to be a serious option in routine clinical practice but its value for women at increased risk is being assessed in a UK trial. Other developments in breast imaging are also being followed with great interest and technological advances could have a major impact in this field within the next decade.

Chemoprophylaxis has obvious attractions and, based on the observation that adjuvant tamoxifen reduces the risk of a second primary breast cancer by some thirty percent, trials of its efficacy in primary prevention have been undertaken in the USA, the UK and Italy. The first of these has been stopped because interim analysis showed a substantial benefit from tamoxifen (48), however, this has not been supported by provisional findings from the other two trials (49-50). The three differed in eligibility criteria, and hence in the representation, among participants, of young women who might be at increased genetic risk. The UK and Italian trials are continuing and a clearer picture may emerge with longer follow-up. In the meantime, new steroidal and non-steroidal oestrogen antagonists are coming on the market. They may offer at least

theoretical advantages over tamoxifen, not least if they lack the tissue-specific agonist effect that confers some increased risk of endometrial cancer.

Prophylactic bilateral mastectomy is a highly emotive topic. Many women do not wish to contemplate this even if they know that they carry a high-risk mutation. On the other hand, a few women are so concerned about their possible risk that they press for surgery without a definitive genetic test. Attitudes must be determined by many factors, including social norms (the Demonstration Programme has revealed striking differences between countries in the demand for prophylactic surgery) and the individual experience of breast cancer among close relatives. The decision to proceed or not should clearly be based on full discussion of all aspects of the genetic risk and the nature of the surgical procedure itself. Where, after appropriate counselling, a woman does decide to undergo total mastectomy (with or without reconstruction) the procedure has a very high success rate in terms of patient satisfaction and data from a large North American series suggest that, when carried out by experienced specialist surgeons, it confers a substantial degree of protection against future development of cancer (51) – perhaps as high as 90%.

Occasionally, cases arise of women who fabricate a family history of breast cancer in a bizarre attempt to secure prophylactic mastectomy for themselves or even for a relative (52). This variant of Munchausen syndrome serves as a reminder of the importance of verifying and extending the reported history as the first step in risk assessment and management.

Prophylactic oophorectomy is considered much more frequently, usually in the context of a family history of ovarian – with or without breast – cancer. Though it is a less radical operation, its protective value is currently uncertain. A proportion of patients develop what appears to be primary carcinoma of the peritoneal epithelium after oophorectomy and it is not clear whether these tumours arise from seedlings of cancer from a microscopic ovarian primary that had already spread or whether cancer susceptibility applies, in some measure, to the whole of the peritoneum (53-54). If the former explanation is correct then there would be a case for early oophorectomy in those at high risk but that raises the vexed question of hormone replacement to counter the symptoms of an induced menopause and the effect of HRT on breast cancer risk. It has been argued that oophorectomy itself is likely to reduce the risk of breast cancer while HRT might tend to reverse that benefit, but not completely. The only study to address this question specifically indicates that, for carriers of BRCA1 mutations, the protective value – against breast cancer – of prophylactic oophorectomy carried out between the ages of forty and fifty (premenopausally), is substantial (up to 50% reduction over the next ten years) and that this protection is not negated by use of HRT (55).

**ECONOMIC ISSUES** It may seem indelicate to introduce financial considerations into a discussion of what are, after all, matters of life and death. Nevertheless, since all health care provision has to be funded from somewhere, it is a reasonable expectation that those promoting any particular development should consider its cost-effectiveness. This, of course, involves much more than the gains and losses in terms of hard cash. Few would argue that a reduction in morbidity and mortality from breast cancer would be a major social gain and that this applies particularly to young women who may be raising children and/or making significant contributions to the economy. As discussed above, the type of risk assessment and surveillance programmes that are evolving in most European countries seem to make a clinically measurable difference and, according to the preliminary calculations from Norway, they do so at modest cost, compared to many other health care interventions (56). A critical question is whether the cost per life year gained would alter substantially if the eligibility criteria for breast cancer family services were changed. At present, most centres adopt a cut-off that corresponds roughly to a 20% lifetime risk of breast cancer but with further experience, it may be possible to define a more "efficient" policy. In fact, it is likely that the intensity of surveillance will be adjusted to the precise level of risk.

This then raises the question of funding for molecular analysis. Setting aside the issue of patent rights over BRCA1 and BRCA2 (57), screening a given family for an unknown mutation is likely to remain expensive for the foreseeable future. At what point is this cost repaid by the reduction in numbers of women who require annual clinical and mammographic surveillance (i.e. through identification of non-carriers)?

Even more opaque (surprisingly) is the calculation of cost-reduction through early detection of breast cancer. Although it is self-evident that a stage I tumour with a high prospect of cure from surgery (with or without adjuvant radiotherapy) is much less expensive to treat than an advanced cancer that may involve repeated surgery and/or radiotherapy, plus complex investigations and multiple courses of chemotherapy. Younger patients are, of course, prime candidates for the most aggressive and expensive regimes. Yet the literature on healthcare costs in these settings is very limited (58-60).

There is a distinct absence of clear answers to most of the economic questions posed. That is a true reflection of our remarkable state of ignorance in such matters and underlines the need for further serious research in this whole area.

## ETHICAL ISSUES

**WHAT IS INFORMED CONSENT?** Given that much clinical practice in the field of familial breast cancer is still, in a sense, experimental, it is right that people attending cancer family clinics

should be aware that we are gaining experience from them and that this will lead to better-informed (and perhaps very different) service provision in the future. Few, if any are upset by this knowledge. Indeed, as in the case of many other genetic disorders, the patients and their families are among the most pro-active in supporting clinical research (61-62), all the more reason for taking care not to exploit their enthusiasm by making assumptions about what is acceptable in terms of data gathering and investigation.

It may seem obvious that identifying the mutation responsible for the pattern of cancer in a given family will open the door to more straightforward decision-making and, eventually perhaps, to effective prevention and/or treatment. However, taking a blood sample with a view to mutation searching (even from an affected member of the family in whom the prediction of carrier status is quite clear cut) should be preceded by a careful explanation of the possible implications for them and their relatives and an opportunity for reflection, before formal consent is obtained or the sample drawn. Practices in this respect seem to vary widely in different centres and different countries. One of the tasks of the EC Demonstration Programme on Clinical Services for Breast Cancer Families will be to see whether a standard protocol for giving relevant information and obtaining valid consent can be drawn up.

The issue is complicated by the fact that mutation searching can be undertaken on archival tissue from deceased family members. In some countries, the next of kin have no legal rights over such tissues, or indeed over the medical records after a patient's death. This raises the possibility of identification of a mutation in a given family before any of the living members are even aware that a study is under way. Such a situation is, at best, undesirable and, again, calls for the development of a consensus on good practice whether or not it has the force of law.

Once a mutation has been identified in a family, there is general agreement that those members who know they may be at risk should be offered counselling with a view to deciding whether or not they will opt for pre-symptomatic genetic testing (63). The presumption is that, at the end of the counselling process they will be in a position to give informed consent for the test (if that is their choice). However, given the uncertainty about penetrance of the cancer trait and the factors that influence it, the question arises do we really know what a positive result means? If we do not, then how can consent for the test be informed. Taking a step backwards, this dilemma applies even more strongly to the initial mutation search. As a rule, permission is sought to search for mutations in any potential breast cancer gene – including those not currently known. There is rarely any time limit placed on the duration of that permission. How can consent be valid for a test that cannot even be envisaged at the time of signing (64)?

Of course this type of argument can be taken to ludicrous extremes that would effectively stultify any clinical research and would operate against the interests of patients. Medical ethics can never be equated to a strict legal framework because the law reacts to events and cannot anticipate developments in science. In any event, medical genetics is full of hard cases and these make bad laws. The best that we can hope for is that health care professionals and patients will continue to look closely at the ethical implications of new discoveries and, together, will work out acceptable courses of action.

**WHAT ARE THE LIMITS ON CONFIDENTIALITY?** The practice of clinical genetics obviously requires information about a given patient's blood relatives. Normally the initial source is the patient him/herself and indeed the taking of a family history is routine in many medical consultations. There is no serious suggestion that this constitutes an invasion of the privacy of the third parties (the relatives); yet if we seek to verify the reported illnesses among relatives we immediately enter dangerous waters. Privacy legislation, which varies in detail from country to country, rightly protects the medical records of any patient and, in general, permission is required from the subject of these records before information can be released. In the UK this protection is substantially reduced with death but in some countries authority for access to medical records passes to the next of kin. Where there is a report that an individual has suffered from cancer, it may be extremely important to verify this in order to provide accurate risk assessment for their relatives but it requires no great feat of imagination to recognise circumstances in which a direct approach to the original patient would cause distress (whether or not the reported diagnosis was correct). On the other hand, the medical authorities responsible for his/her care might consider it a breach of confidentiality if they were to provide information without permission.

It is recognised that the duty of confidentiality is not absolute (65). Where a patient's behaviour constitutes a danger to others then there may be an obligation on the part of the doctor to report relevant medical information to public health authorities or others. What is much less certain is whether a doctor is justified in passing on details of a case history, without the explicit consent of his patient, in order to enhance the medical care of his patient's relatives. Where such an exchange of information is done in good faith and under conditions of medical confidentiality then no harm is likely to result. In that sense then, the behaviour of both the enquiring and the responding doctor is ethical. It can even be postulated that genetic information is not the sole property of any individual but is somehow „collectively" owned by the entire family (66-67). However, until some details of an individual's med-

ical history have been obtained and verified, we cannot know whether it constitutes genetic information or not. Such dilemmas arise, of course, only where the attitude of the relative said to have been affected with the genetic disorder is unknown and in all dealings with families, the preferred route for contacts is through the family members themselves.

A rather different situation may arise when a request for information comes from an employer, an insurance company, a school, an adoption agency or some other third party who may have a legitimate interest in the medical condition or likely future condition of a particular family member. Permission for disclosure in that circumstance must always be sought from the individual concerned and if he/she is a minor then the parent or guardian must be consulted. In the case of familial breast cancer, where onset in childhood is virtually unknown, it is difficult to see any purpose that would be served by disclosing information on the risk status of minors (68).

The attitude of insurance companies to late-onset genetic disease has been widely debated and most at-risk family members are aware that they may be disadvantaged, particularly if they opt for pre-symptomatic molecular testing. The situation must certainly be discussed with them before any decision about testing is taken. In a number of countries, voluntary codes or laws forbid the use of pre-symptomatic test results by insurance companies provided the cover requested does not exceed a certain limit (69-70) and actuarial calculations suggest that the insurance industry can readily absorb the impact of that practice should it be adopted universally (71).

**WHAT ABOUT "THE COUSIN IN AUSTRALIA"?** Whenever a genetic basis for a familial disease cluster becomes clear, questions arise as to how far the trait extends. This is perhaps particularly true of familial breast cancer where most of the identified mutations appear to be ancient and to have been passed down for many generations. The family members attending a given clinic may represent only a small branch of a very large pedigree and may have no personal knowledge of, or contact with, their distant cousins. Nevertheless, especially in countries that have complete and accessible records of births, marriages and deaths, it may be quite easy to construct an extended family tree, from which substantial numbers of at-risk individuals may be identified. Is there a duty on the geneticists providing a service to one branch of such a family to seek out "the cousin in Australia" and advise her of her risk status? At least in the US, the law appears to recognise circumstances in which the duty of care to a third party over-rides the obligation, to a patient, of confidentiality (72). Much depends on the perceived value of that information to the cousin and the perceived disadvantage of remaining in ignorance (73). If the condition is Familial Adenomatous Polyposis, where preventive measures are unquestionably effective, there can be little doubt that efforts to trace all potential carriers are ethical while failure to take reasonable steps to do so would be considered poor practice. The value of intervention in familial breast cancer is not yet so firmly established that the ethical position here is clear. However, if the risk to a traceable relative appears high, and particularly if the mutation in the family has been identified, so that a pre-symptomatic test is available, many geneticists would feel that, at the very least, steps should be taken to offer that relative the opportunity to decide for herself whether she wishes to pursue the question of genetic risk. Where the healthcare system allocates everyone individually to a specific general practitioner, then that physician may be an ideal intermediary between the genetic clinic and the relative but otherwise a letter may be written, inviting her to contact the genetic clinic if she wishes to discuss the family history. In that way information is not forced upon her but neither is it deliberately withheld.

**CONCLUSION** It is obvious that in the field of familial breast cancer we are currently in a phase of very rapid technical advance. Over the next few years we can anticipate the identification of new "breast cancer" genes, clarification of the frequency and clinical consequences of specific mutations and confirmation of the value or otherwise of different approaches to management for those at high risk. As a consequence of these developments, at least some of the social, economic and ethical issues posing such difficulties today may become a little more straightforward.

**REFERENCES**


1. Thompson JA, Wiesner GL, Sellers TA, et al. Genetic services for familial cancer patients: a survey of National Cancer Institute cancer centers. J.Natl Cancer Inst 1995; 87:1446-1455.

2. Campbell H, Mackay J, Porteous M. The future of breast and ovarian cancer clinics. Brit Med J 1995; 311:1584-1585.

3. Broca P. Traite des tumeurs. P Aselin, Paris, 1866.

4. Jacobsen O. Heredity and breast cancer. HK Lewis, London, 1946.

5. Lynch HT, Lynch JF. Breast cancer genetics in an oncology clinic: 328 consecutive patients. Cancer Genet Cytogenet. 1986; 24:369-371.

6. Floderus B, Barlow L, Mack TM. Recall bias in subjective reports of familial cancer. Epidemiology 1990; 1:318-321.

7. Williams WR, Anderson DE. Genetic epidemiology of breast cancer: segregation analysis. Genet Epidemiol 1984; 1:7-20.

8. Bishop DT, Cannon LA, McLellan T, Gardner EJ, Skolnick MH. Segregation and linkage analysis of nine Utah breast cancer pedigrees. Genet Epidemiol 1988; 5:151-169.

9. Go RCP, King M-C, Bailey-Wilson J, et al. Genetic epidemiology of breast cancer in high risk families. 1. Segregation analysis. J Natl Cancer Inst 1983; 71:455-461.

10. Tulinius H, Day NE, Bjarnason O, et al. Familial breast cancer in Iceland. Int J Cancer 1982; 29:365-371.

11. Iselius L, Slack J, Littler M, Morton NE. Genetic epidemiology of breast cancer in Britain. Ann Hum Genet Lond 1991; 55:151-159.

12. Claus EB, Risch N, Thompson D. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet 1991; 48:232-241.

13. Colditz GA, Willett WC, Hunter DJ, et al. Family history, age and risk of breast cancer. JAMA 1993; 270:338-343.

14. Schneider NR, Williams WR, Chaganti RSK. Genetic epidemiology of familial aggregation of cancer. Adv Cancer Res 1986; 47:1-36.

15. Houlston RS, McCarter E, Parbhoo S, et al. Family history and risk of breast cancer. J Med Genet 1992; 29:154-157.

16. Thompson WD. Genetic epidemiology of breast cancer. Cancer 1984; 74:279-287.

17. Kash HM, Holland JC, Halper MS, et al. Psychological distress and surveillance behaviours of women with a family history of breast cancer. J Natl Cancer Inst 1992; 84:24-30.

18. Evans DGR, Burnell LD, Hopwood P, Howell A. Perception of risk in women with a family history of breast cancer. Br J Cancer 1993; 67:612-614.

19. Evans DGR, Blair V, Greenhalgh R, et al. The impact of genetic counselling on risk perception in women with a family history of breast cancer. Br J Cancer 1994; 70:934-938.

20. Lerman C, Kash K, Stefanek M. Young women at increased risk for breast cancer: perceived risk, psychological wellbeing and surveillance behaviour. Monogr Natl Cancer Inst 1994; 16:171-176.

21. Lloyd S, Watson M, Waites B, et al. Familial breast cancer: a controlled study of risk perceptions, psychological morbidity and health beliefs in women attending for genetic counselling. Br J Cancer 1996; 74:482-487.

22. Thirlaway K, Fallowfield L, Nunnerley H, Powles T. Anxiety in women ëat risk of developing breast cancer. Br J Cancer 1996; 73:1422-1424.

23. Bottorff JL, Ratner PA, Johnson JL, et al. Communicating cancer risk information: the challenges of uncertainty. Patient Education Counselling 1998; 33:67-81.

24. Cull A, Anderson EDC, Campbell S, et al. The impact of genetic counselling about breast cancer risk on womenís risk perceptions and levels of distress. Br J Cancer 1999; 78:501-508.

25. Houlston RS. PhD Thesis, University of London, 1992.

26. Bishop DT. Familial predisposition to cancer. Cancer Topics 1992; 10:66-68.

27. Byrd PJ, McConville CM, Cooper P, et al. Mutations revealed by sequencing the 5í half of the gene for ataxia telangiectasia. Hum Mol Genet 1996; 5:145-149.

28. Gayther SA, Warren W, Mazoyer S, et al. Germline mutations of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. Nature Genet 1995; 11:428-433.

29. Gayther SA, Mangion J, Russell P, et al. Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. Nature Genet 1997; 15:103-105.

30. Varley JM, Evans DGR, Birch JM. Li-Fraumeni syndrome – a molecular and clinical review. Br J Cancer 1997; 76:1-14.

31. Thorlacius S, Olafsdottir G, Trygvadottir L, et al. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nature Genet 1996; 13:117-119.

32. Thorlacius S, Sigurdsson S, Bjarnadottir H, et al. Study of a single BRCA2 mutation with high carrier frequency in a small population. Am J Hum Genet 1997; 60:1079-1084.

33. Narod SA, Lynch HT, Conway T, et al. The incidence of cancer is increasing in a large family with hereditary breast-ovarian cancer. Lancet 1993; 341:1101-1102.

34. Steel CM. Cancer of the breast and female reproductive tract. In: Emery and Rimoinís Principles and Practice of Medical Genetics. 3rd edn. Rimoin DL, Connor JM and Pyeritz RE, eds. Churchill Livingstone, New York, 1996; 1501-1523.

35. Narod SA. Genetics of breast and ovarian cancer. Brit Med Bull 1994; 50:656-676.

36. Narod SA, Risch H, Moslehi R, et al. Oral contraceptive use and the risk of hereditary ovarian cancer. N Engl J Med 1998; 339:424-428.

37. Ursin G, Henderson BE, Haile RW, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more then in other women? Cancer Res 1997; 57:3678-3681.

38. Jernstrom H, Lerman C, Ghadirian P, et al. Pregnancy and risk of early breast cancer in carriers of BRCA1 and BRCA2. Lancet 1999; 354:1846-1850.

39. Lynch HT, Lynch J, Conway T, Severin M. Psychological aspects of monitoring high risk women for breast cancer. Cancer 1994; 74:1184-1192.

40. Lerman L, Schwartz M. Adherence and psychological adjustment among women at high risk for breast cancer. Breast Canc Res Trt 1993; 28:145-155.

41. Vasen HFA, Beex LVAM, Cleton FJ, et al. Clinical heterogeneity of breast cancer and its impact on screening protocols: the Dutch experience on 24 families under surveillance. Eur J Cancer 1993; 29A:1111-1114.

42. Saetersdal A, Dorum A, Heimdal K, et al. Inherited predisposition to breast carcinoma. Results of first round examination of 537 women at risk. Anticancer Res 1996; 16:1-4.

43. Lalloo F, Boggis CRM, Evans DGR, et al. Screening by mammography women with a family history of breast cancer. Eur J Cancer 1998: 34:937-940.

44. Kollias J, Sibberling DM, Blamey RW, et al. Screening women aged less than 50 years with a family history of breast cancer. Eur J Cancer 1998; 34:878-883.

45. Moller P, Maehle L, Heimdal K, et al. Prospective findings in breast cancer kindreds: annual incidence according to age, stage at diagnosis, mean sojourn time and incidence rates for contraleteral cancer. Breast 1998; 7:55-58.

46. Moller P, Reis MM, Evans GDR, et al. Efficacy of early diagnosis and treatment in women with a family history of breast cancer. Disease Markers 1999; 16:179-186.

47. Wald N, Frost C, Cuckle H. Breast cancer screening: the current position. Br Med J 1991; 302:845.

48. Fisher B, Costantino JP, Wickerham JL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel project P-1 study. J Natl Cancer Inst 1998; 90:1371-1388.

49. Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen chemoprevention trial. Lancet 1998; 352:98-101.

50. Veronesi U, Maissoneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Lancet 1998; 352:93-97.

51. Hartmann L, Jenkins R, Schaid D, et al. Prophylactic mastectomy: a retrospective cohort analysis. N Engl J Med 1999; 340:77-84.

52. Evans DGR, Kerr B, Foulkes W, et al. False breast cancer history in the cancer family clinic – a report of eight families. Eur J Surg Oncol 1998; 24:275-279.

53. Tobacman JK, Tucker MA, Kase R, et al. Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian cancer prone families. Lancet 1982; 2:795-797.

54. Piver MS, Jishi MF, Tsukada Y, Nava G. Primary pritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. Cancer 1993; 71:2751-2755.

55. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 1999; 91:1475-1479.

56. Heimdal K, Maehle L, Moller P. Costs and benefits of diagnosing familial breast cancer. Disease Markers 1999; 14:167-173.

57. Knoppers BM. Status, sale and patenting of human genetic material: an international survey. Nature Genetics 1999; 22:23-26.

58. de Koening HJ, van Ineveld BM, de Haes JCJM, et al. Advanced breast cancer and its prevention by screening. Br J Cancer 1992; 65:950-955.

59. Richards MA, Braysher S, Gregory WM, Rubens RD. Advanced breast cancer: use of resources and cost implications. Br J Cancer 1993; 67:856-860.

60. Rubens RD. Key issues in the treatment of advanced breast cancer: expectations and outcomes. Pharmacoeconomics 1996; 9:1-17.

61. Hunt A. The patient's viewpoint. Disease Markers 1992; 10:205-210.

62. Zabric V. A patient's perspective on breast cancer and the implications of genetic testing. Disease Markers 1999; 14:133-135.

63. Biesecker B, Boehnke M, Calzone K, et al. Genetic counselling for families with inherited susceptibility to breast and ovarian cancer. JAMA 1993; 269:1970-1974.

64. Panel discussion. Ethical issues in genetic testing. Disease markers 1992; 10:211-218.

65. Reilly P. Legal issues in genetic medicine. In: Emery and Rimoin's Principles and Practice of Medical Genetics. 3rd edn. Rimoin DL, Connor JM and Pyeritz RE, eds. Churchill Livingstone, New York, 1996; 655-666.

66. Royal College of Physicians of London; Report, „ethical issues in clinical genetics". 1991.

67. Pembrey M, Anionwu E. Ethical aspects of genetic screening and diagnosis. In: Emery and Rimoin's Principles and Practice of Medical Genetics. 3rd edn. New York, Churchill Livingstone, 1996; 641-653.

68. Steel CM. Implications of studies of inherited predisposition for prevention and treatment. In: The Genetics of Cancer. Ponder BAJ and Waring MJ, eds. Kluwer Academic, Dordrecht, 1995; 159-176.

69. Ad hoc committee on genetic testing / insurance issues. Background statement: genetic testing and insurance. Am J Hum Genet 1995; 56:327-331.

70. Morrison PJ, Steel CM, Vasen HFA, et al. Insurance implications for individuals with a high risk of breast and ovarian cancer in Europe. Disease Markers 1999; 14:159-165.

71. Macdonald AS. How will improved forecasts of individual lifetimes affect underwriting? Phil Trans Roy Soc Lond B 1997; 352:1067-1075.

72. MacKay RD. Dangerous patients. Third party safety and psychiatrists duties – walking the Tarasoff tightrope. Med Sci Law 1990; 30:52-60.

73. Harris J. The use of information (autonomy and confidentiality). Disease Markers 1992; 10:195-198.