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Genetic Counselling in the Cancer Family Clinic

V. Murday

INTRODUCTION

GENETIC COUNSELLING is the term historically used to describe the interview which occurs when an individual attends a genetic clinic, although this is only part of what actually happens when a patient visits a clinical geneticist. Counselling is important in genetics, and its non-directive nature, offering choices to patients, is the basis of the practice. However, much of the consultation, like any other outpatient appointment, is for diagnosis and management of disease, and this is carried out ordinarily using the history and examination of an affected individual. With genetic disease, it may be the family history that holds the clue to diagnosis, and in a Family Cancer Clinic, diagnosis of a genetic susceptibility to cancer may be largely determined by the family history. Patients are generally referred to the clinic by cancer physicians and surgeons, although a proportion are referred by their General Practitioner, or go of their own volition.

THE FAMILY HISTORY

Establishing the pedigree is an important part of the interview. This is standardised to include the family history of cancer, other diseases, developmental and congenital abnormalities, and a history of miscarriages. At least information about first and second degree relatives should be requested, and, where appropriate, the family history should be extended as far as possible [1].

The age at which cancer was diagnosed, the site(s), and the date of treatment/hospital involved should be ascertained. This will allow assessment of risks to relatives, and confirmation of diagnosis from hospital records. In addition, the diagnosis of a particular cancer syndrome may be possible from the pattern of cancers or associated nonmalignant problems. It is important that the clinician has the necessary background knowledge to recognise any significant pattern, and be able to assess the risks from pedigree analysis.

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ASSESSING THE RISK

As a general rule, the occurrence of the same cancer in three close blood relatives of a family is suggestive that there is a genetic susceptibility, particularly if they were affected at an early age.

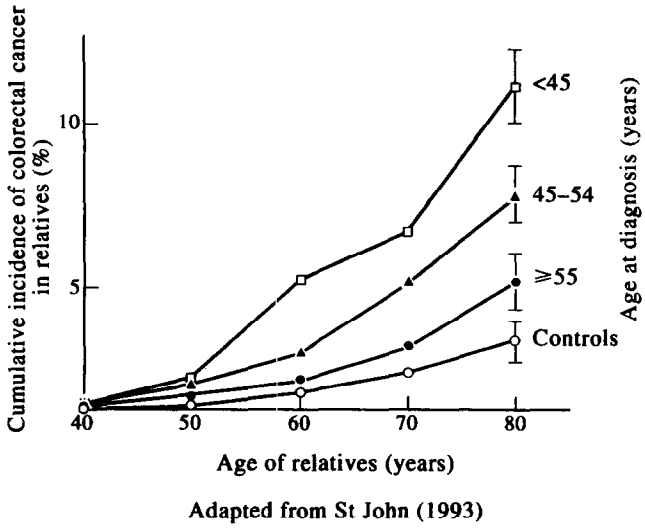
If there are two close relatives with the same cancer, then the population risk of that cancer is an important guide as to the chance of a genetic susceptibility, i.e. if a cancer is rare, then two cases in a family are less likely to have occurred by chance.

Having a single relative with a particular cancer often does not greatly increase the risk to relatives. The exception to this is if the relative is young or had multiple primaries or a recognisable cancer syndrome. The risk of bowel cancer in the relatives of a single case illustrates the importance of age at diagnosis (Figure 1) [2].

Occasionally, a malignancy may be known to occur frequently as a result of a germ line mutation. An example would be retinoblastoma, a rare childhood malignancy of the eye, in which 40% of cases are due to a genetic susceptibility. Some children have multifocal disease, which is almost invariably due to the presence of a germline mutation, with the risk for children of individuals with bilateral disease approaching 50% [3].

Some cancer syndromes have phenotypes that can be diagnosed in an individual. Frequently, it is the premalignant phenotype, such as adenomatous polyps in familial adenomatous polyposis (FAP), that will enable the diagnosis to be made.

There is now published information on the risks for relatives of cancer patients, particularly for common cancers such as breast cancer and colorectal cancer [2, 4–6], these are particularly useful for genetic counselling, permitting visual demonstration of risk assessment to the patient. The likelihood of a genetic susceptibility can be calculated, combining information on the



Adapted from St John (1993)

Figure 1. Cumulative risk of colorectal cancer in relatives of a patient diagnosed at various ages.

number and age of affected individuals. The risk to the patient will depend upon their relationship to the affected family members, and their own age since the risk will decrease the longer they remain free of disease. An example of such a risk assessment for the kindred is illustrated in Figure 2. Table 1 shows the method of combining the information by a simple Baysian calculation to determine the residual risk for the patient.

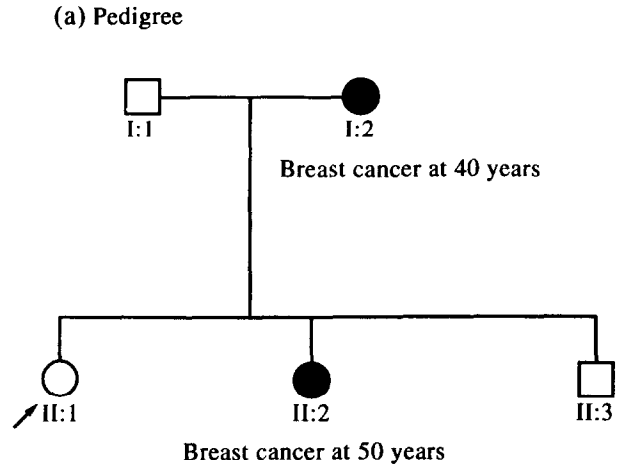
When a specific diagnosis of cancer susceptibility is possible, then there may be more information available to impart, both in terms of the chances of developing cancer and possible non-malignant problems. For instance, if a *BRCA1* mutation is the likely cause of breast cancer in a family, then detailed information is available on the cumulative risk of both ovarian and breast cancer as well as the possibility of other cancers, such as bowel and prostate, for which there is an increased relative risk in affected individuals [6]. A *BRCA1* mutation may be suspected either from the family structure, a dominant susceptibility to early breast cancer associated with ovarian cancer, or by demonstration of linkage to the *BRCA1* region on chromosome 17.

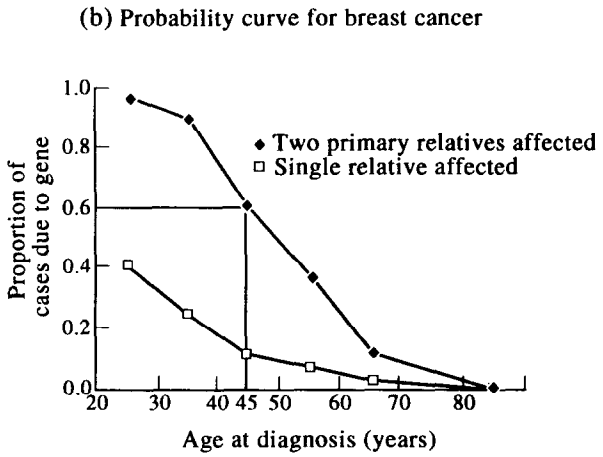
MEDICAL HISTORY AND EXAMINATION

It must be established from the history and examination whether the patient is an affected or an at risk member of the family, and the patient should be questioned on any symptoms indicative of cancer or congenital abnormalities. Initial clinical examination involves looking for any dysmorphic features and congenital anomalies. The skin should be carefully examined as many cancer syndromes are associated with dermatological features, such as pigmentary abnormalities, e.g. freckles are seen in Peutz–Jehjers syndrome, café au lait patches in neurofibromatosis or Turcot's syndrome, basal cell naevi in Gorlin's syndrome etc. Skin tumours, like the epidermoid cysts seen in FAP or keratoacanthomas seen in Muir–Torré or tricholemmas of Cowden's syndrome, should also be investigated.

DISCUSSION OF CANCER SUSCEPTIBILITY AND RISKS

The following part of the interview involves communicating to the patient the results of the pedigree assessment, risk





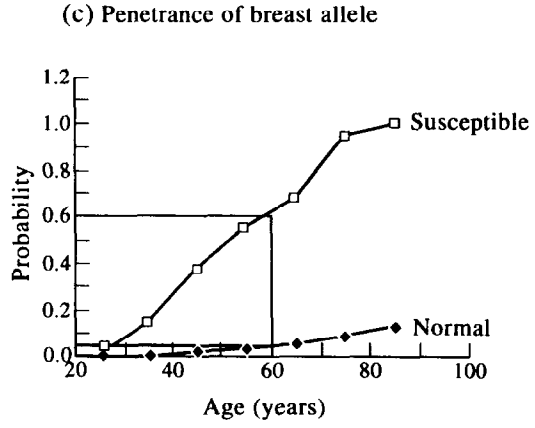


Figure 2. The patient (II : 1 arrowed) has a mother (I : 2) diagnosed with breast cancer at 40 years of age and a sister (II : 2) with breast cancer diagnosed at the age of 50 years (a). Thus, the average age at diagnosis is 45 years and the probability of a dominant gene giving rise to the breast cancer in two primary relatives affected, is 60% (b). Since the woman at risk is a sister or daughter of an affected individual her risk of having the 'gene' is 30%, i.e. 1/2 that of the affected relatives. She is 60 years of age, and by this age, 60% of individuals with the genetic susceptibility will have developed breast cancer (c).

Table 1.

	Susceptible	Not susceptible
Prior probability (from Figure 2(b))	0.30	0.70
Disease-free at 60 years (from Figure 2(c))	0.40	0.96
Posterior probability	0.12	0.672
Residual risk $= \frac{0.12}{(0.12 + 0.672)} = 15\%$		

assessment and clinical examination. If a particular diagnosis is made, then information about the disease can be given.

Those attending genetic clinics may have a very rudimentary knowledge of genetics, and it is important that they have a simple explanation of Mendelian genetics and how their risk has been assessed. A simple explanation of how cancer develops as a result of somatic genetic events is also sometimes helpful. In this way patients can understand and come to trust the information they are given. If they are being given empiric risks then the method by which these figures are derived must be explained. If there are no data, then this must also be discussed, and if the geneticist has a clinical impression that there may be something unusual occurring, but it is no more than a clinical judgement then this must be made clear. Having a risk figure is useful for the clinician as this may dictate what options for management are available, but these are only useful to patients if they are put into context i.e. in relation to the population risk of that and other cancers. In particular, the age at which they are at greatest risk must be discussed, to enable management choices to be made, as these may affect the timing of prophylactic surgery or their cooperation in screening programmes.

Discussion of possibilities for screening and prevention should follow. What is known about the value of any particular strategy including its rationale must be explored. Since some individuals may wish to do nothing, it is important that this is also discussed as an acceptable option, and may be the right decision for some people. In some instances prophylactic surgery needs to be discussed, but this must be approached with caution as some patients are frightened or even horrified at the suggestion. They may feel that this is confirmation from the doctor that their risk of cancer is unacceptably high, and may accentuate any fears they may have of the disease and its treatment.

Throughout the interview, it is important to be sensitive to any psychopathology that may be occurring. Frequently there will have been bereavement due to the premature death of close relatives, particularly a parent. Unresolved bereavement may make it difficult for people to accept their own risks and make decisions on their own management. In addition, patients are sometimes unable to cope with their worries. Referral for formal counselling may resolve these problems. Of particular concern are those individuals who have prophylactic surgery because of excess anxiety but who, while being temporarily relieved, often return at a later date with further cancer phobic symptoms. A psychological assessment and counselling should probably be mandatory before prophylactic mastectomy.

PREDICTIVE TESTING

The number of cancer susceptibilities that have been mapped by genetic linkage is steadily increasing. This allows DNA analysis to be carried out and individuals with a susceptibility gene to be identified before the development of the disease. In late onset genetic disease susceptibilities, there is a consensus view that children should not be tested, unless there is to be a therapeutic intervention or change in management. Some cancer susceptibilities do require screening during childhood. For instance, screening for familial polyposis coli usually starts in early teenage years by sigmoidoscopy. DNA testing prior to this time will allow half the individuals to avoid having this invasive procedure. Testing would therefore seem entirely reasonable, particularly as preventative treatment by prophylactic surgery has been demonstrated as being successful in cancer prevention. The value of testing for other cancer susceptibilities, where the value of screening and prevention is unknown, is less clear cut. Many of the issues that have been discussed at length in relation to testing for other adult onset genetic diseases, such as Huntington's chorea where prevention is not possible, are relevant. It has been demonstrated that using a set protocol for individuals having predictive testing for Huntington's chorea helps to minimise the problems experienced and allows the individual to have time to decide if they really want the test and for what reason [7, 8].

There may be many reasons why individuals may wish to have a predictive test. They may want to know if they have the gene before starting a family, or to make plans for their own future. In other situations, it may be that they want to make choices concerning having prophylactic surgery or entering into screening or chemoprevention studies.

Facing a high risk of breast cancer is particularly difficult for some women. Often there have been several deaths from the disease in the family, and since this is often a mother who has died when the patient was only in her teens, the memories can be particularly painful. Since there may already be a great deal of anxiety about the disease, it may be very traumatic to find that the chance of having the gene for early breast cancer is high. It is therefore recommended that a formal protocol is followed when offering predictive testing for either *BRCA1* or *TP53*. It is probably a good idea to follow these protocols for some of the other more worrying conditions such as von Hippel-Lindau disease. Initially, the pros and cons and accuracy of the test are explained to the patient. There is a compulsory psychological assessment. They are then left to consider for a while whether or not to have the test, and if they decide to proceed, they are seen again to discuss their reasons for wishing to do so. It is only then that the blood sample for testing is collected. The disclosure session is carefully planned so that the patient knows how long they will have to wait for the result. Following this, they are seen at suitable intervals to ensure that they have accepted the result and are not having any problems.

GENETIC HETEROGENEITY

The number of families that can have predictive testing is limited by the degree of genetic heterogeneity, i.e. when more than one locus may cause the same condition. For instance, approximately half the families tested for linkage to *BRCA1* in fact have another gene. Each family becomes an experiment in itself, as linkage must be established in that particular family if predictive testing is to be carried out. The family needs to be large so that there is at least a 95% or more likelihood of linkage. Most families at the moment are not suitable for predictive testing, and patients are often disappointed that they are unable to have the test. Now the gene is identified [9] the number of families that can be tested will increase, since direct mutation analysis of an affected individual will confirm a *BRCA1* family.

Table 2.

Disease	Location	Mutation analysis
Breast ovarian	17q21	Not yet available
von Hippel-Lindau	3p25	YES for *VHL*
Familial adenomatous polyposis	5q21	YES for *APC*
Gorlin's syndrome	9q	Not yet available
MEN Type II	10q11.2	YES for *RET*
MEN Type I	11q	Not yet available
Wilms' tumour	11p13	YES for *WT1*
Retinoblastoma	13q	YES for *RB1*
Li–Fraumeni	17q	YES for *TP53*
NF I	17q11.2	YES for *NF1*
NF II	22q11.2 to q12.1	YES for *NF2*
Lynch syndrome	2p22	YES for *hMSH2*
Lynch syndrome	3p21	YES for *hMLH1*

MEN, multiple endocrine neoplasia; NF, neurofibromatosis.

However, mutation analysis is more labour intensive. A sample is collected from an affected individual and mutation analysis is carried out. Once a mutation is identified, other members of the family can then be tested to see whether or not they carry the mutated gene. Linkage analysis and direct mutation analysis are now possible for many different cancer susceptibilities (Table 2).

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Screening for Cancer Predisposition

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INTRODUCTION

THE LAST 10 years have seen enormous strides in our understanding of events at the molecular level which underlie the development of malignancy. Many examples of potential opportunities for screening provided by these discoveries are presented in articles within this issue. The challenge which now faces us is how to translate this massive body of knowledge into appropriate screening programmes [1, 2] and this challenge is accentuated because the issues involved are enormously complex [3–5]. We will highlight the need for expansion of the academic disciplines contributing to screening for disease predisposition, and the attendant public health questions raised [6]. The need for research prior to provision of services of this type is always underestimated, and the resources required will always tend to be large because of the expense involved in most epidemiological studies [7]. Detailed economic assessment of health gain to be anticipated from cancer predisposition screening must be undertaken [8]. It is important that we clearly understand where cancer screening stands now, and how it might best be further developed in the future, in the most cost effective manner [9]. This whole area remains highly controversial, mainly because financial calculations are very soft and are not necessarily universally applicable. The additional diagnostic yield which may be possible, based on our new molecular knowledge, must be seen as something to add to and dovetail with current cancer screening programmes, and not as a separate entity in itself.

Whilst we focus here on problems in genetic screening for cancer predisposition [10–12], we should not lose sight of the fact that total population screening is likely to remain the major contributor to reducing cancer morbidity and mortality in industrialised populations [2]. Whilst the systems are by no means perfect, the probability is that screening will continue to be our major weapon in the fight against cancer indefinitely because the development of curative therapeutic modalities for advanced disease is highly unlikely in the foreseeable future. Even if such agents become available, the earliest possible diagnosis will remain desirable to reduce morbidity. Thus, our major hope for reducing the disease burden overall is in either preventing it happening in the first place or in finding and

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