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Editorial

Cancer Genetics Clinics

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There has been a huge increase in interest in genetic predisposition to cancer since the localisation and finally isolation of genes predisposing to bowel, breast and ovarian cancer [1–4]. Although up to 10% of these cancers have a strong familial element, it is only possible to identify a definite dominant pattern of inheritance in approximately 1% of individuals presenting with these cancers. There is still a great deal of debate as to whether genes such as *BRCA1* and *BRCA2* in breast cancer and the DNA mismatch repair genes in bowel cancer account for just a small proportion of the total familial element. It is possible that they account simply for the highly penetrant susceptibility alone (this is after all the group of families that led to their isolation). It is, nonetheless, still possible that they account for a greater proportion, as previously predicted from epidemiological studies [5]. Therefore, these genes could account for as little as 1% or as much as 5–10% of all bowel, breast and ovarian cancers. We will have to await large epidemiological studies of unbiased series of these cancers before the true contribution of these genes to cancer is known. Nevertheless, the great majority of individuals who perceive themselves to be at risk of cancer will not be at risk of inheriting these highly penetrant genes. Nonetheless, as over 26000 women are diagnosed with breast cancer in the U.K. every year, the potential burden on cancer genetics clinics is massive.

The interest in genetic testing is fast gathering pace and, inevitably, many individuals at little or no increased risk of cancer are asking about these tests, as well as for a definition of their own risks and to discuss preventive and screening options. Even if this group were confined to those with a family history of one or more common malignancies, this would be impossible to manage in specialist clinics. The publicity surrounding familial cancer and particularly breast cancer, has led to an increasing demand for information, not just from individuals with a family history of cancer, but also by their clinicians. Up until recently, this demand was met largely by individuals being seen on an *ad hoc* basis in general surgical, medical, oncological or genetics clinics by interested clinicians. The demand is now so great that specialist family history clinics have been set up throughout the U.K. and Europe to manage the more familial common cancers (bowel, breast, ovary). These clinics are often run jointly by a geneticist and an interested clinician, usually one involved in the screening and or surgery for the established cancer or pre-cancer conditions. Thus, the client attending the clinic is able to obtain information on their genetic risk of certain cancers and also have access to expert screening and other advice. A growing number of families are now accessible to specific genetic tests which will predict who actually carries the predisposing gene. This has opened up a new debate on the ethics of genetic testing for cancer predisposing genes and the psychological consequences of the tests. Because of the expertise required for accurate risk estimation and counselling for predictive testing, these should probably only be offered through experienced clinics.

THE CANCER FAMILY HISTORY CLINICS

The concept of a specialist clinic to counsel individuals at risk of cancer and screen them for the disease is not a new one. A clinic set up to screen families with familial adenomatous polyposis (FAP) has been functioning since the early part of this century at St Mark's Hospital in London. Indeed, genetic registers for FAP, von Hippel Lindau disease, neurofibromatosis types 1 and 2, Gorlin syndrome and various other dominantly inherited tumour predisposing conditions are well established. These are usually centred on genetics departments which organise or co-ordinate the various screening protocols and arrange the relevant DNA predictive tests which now exist for virtually all of these conditions. The rationale for counselling and screening in the phenotypic syndromes is unquestioned. However, the situation is less clear when we examine the more ill defined predisposition to common cancer. The now unequivocal evidence for highly penetrant dominant genes predisposing to breast, bowel and ovarian cancer would justify this in terms of genetic counselling and risk estimation. However, only a few families show a clear pattern of inheritance consistent with a 50% chance of inheriting such a gene. This means that in most instances epidemiological studies have to be consulted in order to estimate risk [5, 6].

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Having arrived at an estimate of risk for an individual it is then necessary to examine the options for early detection (screening) and prevention. Screening has been advocated for breast, bowel, ovarian cancer and melanoma, but is probably not justified in most other common malignancies. In spite of the very high risk under the age of 50 years in breast cancer families, screening with mammography is still controversial, as it is not proven to be effective in this age group. Nonetheless, most clinics would recommend this from approximately 35 years of age on an annual basis. Equally, ovarian screening with ultrasound or biomarkers such as CA125 appears promising, but is not yet proven to be effective. Endoscopic screening of the bowel is probably the most effective screening in this category as it is potentially preventative by removing the premalignant adenomatous polyps.

The age-specific risk for each individual has to be correlated with the cost and effectiveness of the available screening to determine a plan for that person.

RISK CALCULATION AND CONVEYANCE

Most cancers are associated with an elevated risk of the same cancer and sometimes others (for instance ovarian cancer risk is increased in relatives of women who have breast cancer) in first degree relatives of an index case. However, it is only in the cancers with a larger hereditary component that this risk becomes important. Clinicians will also largely confine themselves to diseases which are amenable to screening or prevention, so that there is a "benefit" for conveying possibly worrying information to relatives about their risks. Risks can be calculated from Mendelian models for those with a clear pattern of inheritance, or in families with a proven mutation (eg *BRCA1*), or empirically from population studies [5].

As the article by Julian-Reynier and associates (pp. 398–403) in this issue correctly mentions, little has been published about cancer genetic clinics, except on risk perception and potential uptake of genetic testing. There is, however, a burgeoning body of researchers in psychology and sociology who are studying this area. The accepted belief among many of them is that individuals do not want information about risks, but about how to get screening or prevent cancer. This French study which contains only one third who initiated their own referral still shows that over 60% of individuals expect to have information on risk. Our own work in Manchester suggests that an even higher proportion want this information. It would appear that referring clinicians also have a reasonably good idea about who warrants referral, although those sending patients to these fairly new clinics are likely to be the best informed.

TARGETED SCREENING

In the U.K. the only generally available screening for cancer is cervical screening, and breast screening with mammography from 50 years of age. The latter screening is "targeted" in that it is aimed at the higher risk group in the general population (older women). The cancer family history clinic enables targeting of a second high risk group; those with a family history of cancer. Referral to a cancer genetics clinic is likely to raise expectation that the individual will be eligible for such screening or preventive options. It is not clear from the French study what proportion of consultees would have been eligible. However, at least 25% would have been disappointed as they were either at no increased risk or the geneticist was not sure. Unless the geneticist can fully reassure the individual about their status, this may lead to increased anxiety on top of that engendered by waiting for a cancer genetic appointment. It is important that this group is identified early and reassured, preferably before an appointment for the clinic is made. This could be achieved either by better education of primary health care clinicians and the equivalent specialists, or by sifting out these referrals early in the process.

PSYCHOLOGICAL IMPLICATIONS

The duty of the clinician/counsellor is first of all to do no harm (non-beneficence). The secondary aim is for the whole process, be it risk counselling, screening or a genetic test, to be of some benefit (beneficence). The psychological impact of attending clinics is being assessed and in the U.K. at least, appears, if anything, to cause a slight reduction in anxiety. The impact of genetic testing still needs to be fully evaluated, particularly for conditions where little can be done (Li–Fraumeni syndrome), to ensure no long-term overall harm is caused by the counselling process or genetic testing.

While response to the direct approach of an individual or family is perfectly reasonable, there is still no strong evidence to support chasing up family members for screening that is currently of unproven benefit. The same could be said for a clinician who identifies a family history and suggests referral to a cancer genetics clinic. It is also important that clinicians in general are aware of the present limitations of genetic testing. Given the heterogeneity of predisposition to cancer and the inability to detect all causative mutations, testing should only be offered to unaffected individuals when a mutation has been found in an affected family member. Even then there are still doubts as to the implications of specific mutations in genes such as *BRCA1*.

Clearly each cancer predisposition syndrome will have to be considered on its own merits with counselling on the implications of testing in pregnancy, childhood and indeed at any age for the individual and family requesting, or being offered testing. A full support service should be in place with follow up not only of unfavourable, but also of low risk predictive results.

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