Familial Breast and Ovarian Cancer

Genetics, Screening and Management

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Introduction

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It has long been recognized that some very rare forms of cancer, such as retinoblastoma and neurofibromatosis, are caused by inherited genes. It is only within the last few years, however, that rapid progress has been made in understanding the role that inherited genes also play in determining a proportion of the more common cancers, including breast, colorectal and ovarian cancer. Although there is still uncertainty about the precise contribution of inherited predisposition genes to the incidence of these cancers, the available evidence suggests that breast, colorectal and ovarian cancer have a number of common genetic features.

- A small proportion of these cancers (about 5%) are caused by inherited genes which, though comparatively rare, confer very high lifetime risks of developing cancer. In some cases these lifetime risks may be as high as 80%.
- Cancers caused by these high penetrance genes are more likely to occur at an early age than sporadic cancers, and 15–20% of the cancers diagnosed in people under the age of 50 years may be accounted for by these genetic mutations.
- Carriers of known genetic mutations, which confer high lifetime risks of developing breast or ovarian cancer, are also at significantly increased risk of developing certain other forms of cancer.
- A further 10–20% of breast, ovarian and colorectal cancers are likely to be caused by inherited polymorphisms in predisposition genes, which are commoner but less penetrant but which confer some increased risk (more than three times the general population risk). These 'medium risk' genes have not yet been clearly identified.
- Familial clustering of the more common cancers may also be influenced by environmental and lifestyle factors as well as by chance.

Services for cancer genetics

Cancer genetics is a new field and the organization of services in this area may be initiated by clinical genetics services or through oncology and other departments,

where individuals with a special interest in cancer genetics arrange to see individuals with a family history of cancer, estimate their cancer risks and arrange surveillance and genetic testing as appropriate.

In many parts of Europe, cancer genetics clinics have been established for many years, and most specialized genetic counselling for cancer susceptibility is organized from genetics centres. However, the organization and quality of such services vary, depending on the economic status and healthcare systems of the country. There is increasing awareness that education and referral guidelines for primary care physicians are important. This would allow a collaborative relationship to be developed with primary healthcare services, helping them act as gatekeepers for the prioritization of referrals for genetics services.

Growing public awareness of the familial risks of cancer has led to a rapid increase in demand for advice about these risks and in the number of referrals to genetics clinics in all parts of Europe. Many of these clinics lack the resources to meet this demand and as a result of this and a desire to provide the 'best' service possible to high-risk patients, clinics need to ensure that the service they provide is evidence based. Where evidence is lacking, an audit of 'best practice' guidelines is essential to provide the information. In order to obtain sufficient information, a very large cohort of at-risk individuals, well documented for family history, needs to be followed up for many years. Such an audit is only possible with large multicentre trials, and the emerging European and North American collaborations are an ideal forum for this.

The basic aims of genetic services for people concerned about familial risks of breast or ovarian cancer are: (1) to provide advice and counselling about familial risks, and (2) to identify those who are at an increased risk. Where possible, molecular tests for mutations in genes such as *BRCA1* and *BRCA2* may be possible, and predictive testing will allow the identification of very-high-risk individuals. Once identified, these individuals will need to be enrolled in effective protocols for the management of their risk and for the treatment of cancers detected. Large-scale evaluation of such management is facilitated by European collaborative studies.

This collection of chapters sets out guidelines for assessing whether individuals are at an increased risk of developing cancer on the basis of their family history. The initial point of contact for many individuals concerned about familial cancer risks is the family doctor. Hence guidelines could be provided to family doctors and their staff to assist them in the assessment of risks. Individuals considered to be at sufficiently high risk could be referred to genetics clinics, where a more detailed assessment would be carried out.

Individuals who are assessed as being at an increased risk of developing cancer, but often where no *BRCA1* or *BRCA2* mutation can be identified, should be

offered regular screening. Suggested screening protocols for the management of these individuals, covering the age range, frequency and type of screening, are outlined in chapters benefiting from the collective experience of groups from many European countries and from the USA and Canada.

Cancer genetics is an area where medical knowledge is developing rapidly, and there will be a continuing need to assess the implications of new research into the genetic aspects of breast and ovarian cancer for the screening programmes currently recommended. The implications of research into the genetic aspects of other forms of cancer may also need to be assessed. The benefit of the experience of different countries and cultures in implementing the health strategies suggested by the results of such research is important.

Eleven centres in Europe worked together from 1997 on an EU-funded demonstration project entitled: 'Familial Breast Cancer: Audit of a New Development in Medical Practice in European Centres'.

The chapters included in this book were generated, in part, from the work of this project and provide guidelines, evidence and consensus views for a variety of aspects of patient care within a cancer genetics clinic. The other chapters originate from colleagues worldwide who are providing evidence in other areas of cancer genetics on which patient care can be based.

As a final outcome of the EU demonstration project, the 'International Collaborative Group on Familial Breast and Ovarian Cancer' was established. This worldwide group will continue the work of the project and will, in addition, collaborate and integrate with other groups and individuals who share a common interest in producing evidence to develop our understanding of the inherited cancers and hence improve the care of patients and their families.