Genetic counselling in breast and colorectal cancer

P. A. Daly

Department of Haematology and Oncology, St James’s Hospital and Trinity College, Dublin 8, Ireland

Introduction

Although from antiquity, and particularly through the 19th and 20th centuries, some consistently held that there was a significant contribution of inherited predisposition to the incidence of common cancers, this has only been generally accepted within the past 20 years [1, 2]. The demonstration of genetic linkage in families with multiple cases of cancer, particularly breast and ovarian cancer but also colorectal and other cancers, changed thinking on this matter [3–5]. Strongly predisposing mutations identified by linkage analysis and positional cloning are, however, relatively rare. At most they account for 5–10% of cancer incidence among common cancers such as colorectal, breast and ovarian cancer. Such findings have been useful in the management of families with inherited cancer predisposition, and have also provided important insights into cancer biology. Much more remains to be learned about inherited effects given that the highly penetrant mutations in genes already discovered account for a small fraction of the total effect of inheritance.

Further inherited cancer predisposition is most likely polygenic if modelling is based on epidemiological studies, and this polygenic model suggests that there is a wide range of susceptibility to cancer in the population [6]. It is suggested that some inherit a range of genetic variants associated with low cancer risk while others inheriting a different gene profile may have a much higher than average risk. It is likely that the majority of genes which, when they contain mutations, are associated with high cancer risk have now been identified. In the coming years, while further such genes may be discovered, much focus will be put on the identification of genes whose combined effects contribute to the majority of cancer predisposition.

Despite this, much information has been gathered that can be applied to cancer management and which can help to reduce the number of cancer deaths. Cancer genetics is rapidly becoming a mainstream activity within cancer care, and is particularly important in the management of colorectal cancer, breast cancer and ovarian cancer [7, 8].

Colorectal cancer is among the three most common cancers in Europe and North America and when there is an inherited predisposition, identification of the mutation in a patient offers the opportunity to identify other family members at risk who can have an excellent chance of disease prevention or early detection, thereby leading to a reduction in cancer deaths [9, 10].

Breast and ovarian cancer too are among the leading cancers affecting women. A similar approach can also lead to a reduction in cancer deaths, though interventions, other than prophylactic oophorectomy, have less-proven efficacy than those available in the field of colorectal cancer [7, 11, 12].

Defining inherited cancer predisposition

If resources are to be appropriately used and specialist services directed towards those who need them in the area of cancer genetics, a major challenge is to accurately define those families who have a high-risk, inherited predisposition and separate them from the vast majority for whom risks are low. To achieve this we must, in the main, rely on clinical features that alert to the possibility of high-risk inherited predisposition. These include young age at onset, multiple tumours in an individual, bilateral disease in paired organs and particularly the occurrence of cancers in close relatives. In general, compiling a family history in a detailed fashion gives the basis for identification of inherited cancer syndromes. Information should be gathered on at least three generations, the cancer cases within these families should be clearly documented and, where possible, confirmed through pathology records and death certificates. Details on unaffected family members should be recorded as well, as they may well represent people at risk and their inclusion will also be important in identifying the inheritance pattern, which is usually autosomal dominant.

Knowledge of rare clinical syndromes that show Mendelian inheritance is also important, and these are listed in Tables 1 and 2. Precursor lesions such as polyps should be noted, as well as a record of ethnic origin since founder mutations are known to exist in certain populations such as those of Ashkenazi descent [13].

The provision of an organised service to patients and families in the field of cancer genetics poses a major challenge. Where health service delivery is based on national planning rather than being consumer-led this is, in theory, somewhat easier to structure. Multidisciplinary teamwork involving the relevant clinical specialities, notably genetics
Table 1. Genetic predisposition to colorectal cancer: syndromes, risk and cancer burden

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene/chromosome</th>
<th>Lifetime cancer risk (%)</th>
<th>Percent of new cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPCC</td>
<td>MLH1/3p</td>
<td>80</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>MSH2/2p</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSH6/2p</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PMS1/2q</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PMS2/7q</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MLH3/14q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAP</td>
<td>APC/5q</td>
<td>100</td>
<td>0.1–0.5</td>
</tr>
<tr>
<td>JP</td>
<td>SMAD4/18q</td>
<td>50</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td></td>
<td>BMP1A/10q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-JP</td>
<td>LKB1/19p</td>
<td>10</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>MYHP</td>
<td>MYH/1p</td>
<td>Uncertain</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer; FAP, familial adenomatous polyposis; JP, juvenile polyposis; P-JP, Peutz–Jeghers polyposis; MYHP, MYH polyposis.

AfterJarvinen[1].

Table 2. Genetic predisposition to breast cancer: syndromes, risk and cancer burden

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene/chromosomes</th>
<th>Lifetime cancer risk (%)</th>
<th>Percent of new cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast/ovarian</td>
<td>BRCA1/17q</td>
<td>Up to 85</td>
<td>3.0</td>
</tr>
<tr>
<td>Breast/ovarian</td>
<td>BRCA2/13q</td>
<td>Up to 80</td>
<td>3.0</td>
</tr>
<tr>
<td>Li–Fraumeni</td>
<td>TP53/17p</td>
<td>Up to 90</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM/11q</td>
<td>Up to 60</td>
<td>Debated</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>PTEN/10q</td>
<td>20–50</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>HNPCC</td>
<td>MLH1/3p</td>
<td>Unknown</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>HNPCC</td>
<td>MSH2/2p</td>
<td>Unknown</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>CHEK2-related</td>
<td>CHEK2/22q</td>
<td>Unknown</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer.

services, medical and surgical oncologists and primary care workers, is essential. Ideally each discipline will have guidelines outlining their relevant roles. At present the most important dimension is to select out those high-risk individuals and families so that specialist services can be focused on their needs and scarce resources used optimally in their interests.

Genetic counselling

As with others involved in medical care, medical oncologists through the years will have been familiar with the term ‘genetic counselling’. However, it means different things to different people, and some would see it as supportive or psychotherapeutic such as a counselling process in the social field. Others see it as something rarely applied in a small number of inherited diseases or involving complex mathematics towards estimation of inheritance risk. An older definition [14] described genetics counselling as: ‘an educational process that seeks to assist affected and/or at risk individuals to understand the nature of the genetic disorder, its transmission and the options open to them in management and family planning.’ A more modern and commonly used definition is: ‘genetic counselling is the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and the ways which this may be prevented, avoided or ameliorated’ [15]. Within these definitions the supportive or psychotherapeutic role is implied and, though delivered as a component, it is not the core activity of genetic counselling. In the oncology field the main elements of genetic counselling can be summarized as:

- The documentation of family information and pedigree construction
- The cancers within a syndrome to which a predisposition may exist
- Their clinical features and diagnosis
- Recognition of inheritance patterns and risk estimation
- Communication and empathy with those being seen
- The provision of information on available options and further measures
- Support in decision-making and for decisions made
- Arranging of care for those at high risk

Informed consent for the individual going through the genetic counselling process is a dominant consideration. Genetic counselling is time intensive and depends on accurate data gathering. Ultimately, it provides personal risk assessment for individuals who present, and discusses and addresses the multiple issues outlined above with them. It is vital that sufficient time is allocated and that a full discussion takes place. The motivation of the individual for attendance should be assessed. Peoples’ perception of risk varies and their wishes with regard to the definition of risk and how it is to be conveyed should be determined. It is important too to consider the timing of the visit that may have been provoked by events that have occurred within the family in the past such as deaths from cancer or anniversaries associated with cancer development and death. In general, children should not be involved in the process unless this is specifically indicated where there is a risk of cancer onset in childhood. Genetic screening of DNA for inherited mutations is often laborious and slow, although the time-scale for many of the more common syndromes is now improving. In general, screening for a mutation is undertaken on a blood sample from a live, affected individual. The goals in screening for a mutation are to detect a mutation that will guide the future care of the individual being tested but which will also offer the opportunity for relatives, affected or unaffected, to have predictive testing to determine whether or not they carry the deleterious gene copy. Models exist that will predict the risk for breast/ovarian and colorectal cancers [16–18]. Some of these describe the risk of developing cancer while other models assess the risk of harbouring a mutation in a specific gene. In general only a minority of those screened
will be proven to have a deleterious mutation in one of the highly penetrant, cancer predisposition genes [2].

It is therefore common to have a negative result when an individual opts for genetic screening. The explanations for this are as follows. First, a mutation may truly not be present; secondly, for technical reasons a mutation may exist but may not have been found; and thirdly, a mutation may exist in a gene or genes yet to be identified to confer cancer predisposition. It is important that individuals undergoing genetic screening understand these uncertainties from the outset, and discussions with them should include options for risk estimation without genetic screening. All genetic testing should be explained in terms of indication, accuracy and, where appropriate, possible cost. People should know too that an indeterminate result may emerge, as well as a result that can be interpreted as positive or negative. It is vital to ensure that each individual is clear on these issues before genetic testing is undertaken.

When a deleterious mutation has been detected in an affected family member, blood relatives of that person can opt for predictive testing. The individual needs to be advised of the risks associated with such mutations prior to having predictive testing. Predictive testing may have implications for other family members as well as for the individual opting to be tested. One such issue is that of unwanted disclosure of another individual’s genotype. This may occur for instance where the niece of an affected individual is tested and proves positive, thereby identifying a parent as a carrier. Those who opt for testing and who remain unaffected need to be counselled as to how they might cope with learning that they are at high-risk of developing malignancy. They need to review too how they might react to good news and how that might affect the family dynamic. For young people particularly it is wise to advise them to seek financial advice before proceeding. This is to ensure that they avoid, where possible, discrimination in terms of insurance cover [19, 20].

The genetic testing process may be associated with significant psychological distress. To avoid or minimise this it is advised that the process of predictive testing should be delivered through a protocol requiring three sessions of counselling [21]. At the first session information is provided with a discussion of family history, the potential risks of malignancy and the applicability of screening programmes and other useful interventions. At the second session a discussion of predictive testing is undertaken and at the third session, if all are agreed, a blood sample is drawn. A delay of 1 month is advised between the second and third sessions. This ensures that the individual has had sufficient time to consider predictive testing and to discuss their decision with other family members or friends. It is appropriate too that the second and third sessions are initiated by the patient and not by the medical carers. People need to understand that testing can be undertaken at any time in the future and that, provided appropriate medical care is being delivered, delay is not inappropriate. When receiving results the patient should attend in person with support, and only in exceptional circumstances should a result be delivered other than in this fashion. This process may appear tedious but it is based on the genetic counselling process in other areas such as Huntington’s disease and has been shown to be safe and effective. Patients should be informed of the protocol for predictive testing at the outset and should be given an approximate time span from the initial appointment to the provision of a result.

Colorectal cancer

Colorectal cancer is a common malignancy in the developed world, and in Europe has an annual incidence of ~30 per 100,000. The disease is uncommon in Africa, Asia and South America, and dietary factors have long been suggested to be involved in aetiology. This issue, however, remains unclear. Colon cancers generally occur on the left side of the colon and the presentation of a tumour in the right colon should suggest the possibility of an inherited predisposition [8]. More than 50% of the general population will have adenomatous polyps by the age of 70 years and most cancers appear to develop from such adenomas. While lifestyle and environmental factors contribute mainly to the pathogenesis of sporadic colorectal cancer, between 5% and 15% of cases will develop on the basis of underlying genetic predisposition. Such predisposition is often the result of a highly penetrant mutation in a single gene. Such a germ-line mutation will lead to cancer occurring at a much earlier age than sporadic cases, and identification of the hereditary trait will offer an excellent chance for prevention or early detection in other family members through appropriate genetic care, endoscopic surveillance and sometimes through prophylactic surgery [9, 10]. Cancer predisposition may be inherited in the context of hereditary non-polyposis colorectal cancer (HNPPC) syndrome, which is characterised by the development of colorectal cancer without preceding multiple adenomas, although solitary or sparse adenomas are the usual precursor lesions in this condition. Genetic predisposition is also associated with multiple polyposis syndromes.

Hereditary non-polyposis colorectal cancer

The clinical features of HNPPC [Mendelian inheritance in man (MIM) No. 120435(MSH2); 120436 (MLH1)] include an increased tendency to develop colorectal cancer at an early age, at an average of ~40 years. Tumours have an increased incidence in the right colon and are frequently multiple and arise from adenomatous polyps. These polyps are few in number. For known gene mutation carriers the lifetime risk of bowel cancer is ~80% in men and 40–60% in women. Women, however, have the added risk of endometrial cancer of ~40–50% during their lifetime. Other cancers of which there is increased risk are cancer of the ovary, stomach, small intestine, renal and biliary tracts. Transitional cell cancers of the ureter also occur in this context. The usual diagnostic criteria used are the modified Amsterdam criteria [22]. These are: at least three relatives with an associated HNPPC, one of whom must be a first degree relative to the other two, at least
two successive generations should be affected and one of the affected cases must have been diagnosed before the age of 50 years. Tumour pathology should be verified and familial adenomatous polyposis (FAP) must be excluded before this diagnosis is made. Some hold that these criteria are too strict and that HNPCC should be suspected on the basis of a less rigid definition [8].

Since the age of onset is between 25 and 60 years, screening should be practiced from an early age [19] and known gene carriers should be offered colonoscopy every 12–18 months from the age of 25–30 years. Those at 50% risk or fulfilling the Amsterdam criteria should be offered screening on a 2-yearly basis. At risk women should have transvaginal ultrasound and hysteroscopy with pipette biopsy yearly as screening for endometrial cancer. Screening for transitional cell carcinoma has also been advocated using annual urine microscopy. Colonoscopic screening with polypectomy has been shown to reduce colorectal cancer incidence by >60%, to prevent cancer deaths and to improve overall survival. In addition prophylactic hysterectomy, salpingo-oophorectomy and colectomy are additional options that are thought to be effective, but are unproven in randomised clinical trials.

The mismatch repair genes involved are described in Table 1. The majority of mutations occur in the MSH2 and MLH1 genes. Mutations span the entire gene sequence but two specific mutations account for 63% of HNPCC families in Finland. Only a very small number of mutations in PMS2 and one in PMS1 have been reported. Endometrial malignancy is thought to have a greater frequency with MSH6 mutations. Expressed proteins from the mismatch repair genes recognise mismatched base pairs, excise them and replace them with the correct nucleotides. When this process does not function properly replication errors result in genetic instability and regions of DNA composed of short repeated sequences are characteristically altered. This gives rise to the entity known as microsatellite instability (MSI). As a result of this, somatic mutations may arise in unstable genes during tumourigenesis with acceleration of tumour progression and early onset of malignancy. Mutations affect protein–protein and protein–DNA interactions.

Screening for a mutation in the context of HNPCC is still a long and laborious process. If a family fulfils the modified Amsterdam criteria, screening for a mutation should proceed. When families do not fulfil these criteria a tumour block from an affected individual should be sent for MSI testing. If a high level of MSI is detected (instability at two or more out of five loci or at ≥30–40% of studied loci), mutation screening of DNA should proceed. If a mutation is identified predictive testing can then be offered to adult blood relatives to facilitate targeted screening. The modified Amsterdam criteria are listed in Table 3 and should guide this process [23].

### Polyposis syndromes

**Familial adenomatous polyposis**

FAP (MIM No. 175100) is characterised by at least 100 adenomatous polyps in the colon and rectum, but an attenuated form with far fewer adenomas has been described. The association of medulloblastoma with FAP has been termed Turcot syndrome (MIM No. 176300). FAP is a rare disease with an incidence of ~1–2 per million people per annum. Up to 50% of these are new mutations in the APC gene. In other circumstances, several family members will be affected. The APC gene is located on chromosome 5q and an APC mutation can be detected in >60% of families affected with FAP. A proportion of the remaining families are explained on the basis of mutations in the MYH gene, especially when the attenuated form is present [24]. Further genetic causes for this condition remain to be discovered.

FAP is defined on the basis of endoscopy and family history. Genetic diagnosis is confirmed by the finding of a mutation in the APC gene. Further clinical features that may be present include epidermoid cysts, osteomas of the jaws, desmoid tumours, fundal gastric polyps and congenital hypertrophy of retinal pigment epithelium.

In the context of FAP, malignancy will develop in one or more adenomas with a mean age of onset of 40 years. The adenomas begin to appear at puberty and with their increase in number and size are associated with symptoms including diarrhoea, rectal bleeding and often the features of anaemia. When symptomatic, 60% of FAP patients will already have developed malignancy.

In terms of prevention, however, if fibreoptic sigmoidoscopy is offered to the children of an FAP parent from the age of 12–15 years, the diagnosis can be established before the onset of cancer. Where there is a known APC mutation in a family, predictive testing can be offered and, if accepted, at-risk individuals can be identified and surveillance concentrated on those.

The appropriate treatment for FAP is prophylactic colectomy, which should be performed at the age of 20–25 years. Surgical options include colectomy with ileorectal anastomosis with lifetime surveillance of the rectal stump or proctocolectomy with ilea pouch-anal anastomosis. The latter has a risk of poorer anal function but is not associated with cancer risk in the rectal stump, which is up to 15% over 20–25 years. Unfortunately, there is continuing risk of duodenal cancer and also desmoid tumours, which are extremely difficult to treat. Application of prophylactic surgery, however, as outlined above has given survival outcomes comparable to those of the general population [9, 25].
Juvenile polyposis

Juvenile polyposis (JP) (MIM No. 174900, 17505) is a very rare syndrome with a frequency of about one-tenth of FAP. It is caused by mutations in at least two separate genes: SMAD4/DPC4 on chromosome 18q and BMPRIA/ALK3 on chromosome 10q [26, 27]. Inheritance is autosomal dominant. The proteins encoded by the SMAD4 gene and the BMPRIA, if mutated, disrupt two separate elements of bone morphogenetic protein (BMP) signalling, and this results in the phenotype described.

It is characterised by multiple hamartomatous polyps that are histologically different from those found in Peutz–Jeghers syndrome (P-JS). Clinical symptoms include abdominal pain, features of anaemia, intussusception, chronic bleeding from the bowel and failure to thrive. Polyps occur in the colon and small bowel and also in the stomach. The lifetime risk of gastrointestinal malignancy is ~50%.

Treatment of JP [28] consists of repeated endoscopic removal of all polyps detected in the colon or upper gastrointestinal tract. Endoscopy should be performed at 2-year intervals. Where there is a high number of colonic polyps, colectomy with ileorectal anastomosis is appropriate. This treatment is aimed at decreasing the cancer risk and preventing symptoms such as those outlined above.

At present mutation screening is available on a research basis only.

Peutz–Jeghers syndrome

P-JS (MIM No. 175200) is another rare polyposis syndrome transmitted in an autosomal dominant fashion and associated with mutations in the STK11 (LKB1) gene on chromosome 19p [29]. The function of the protein encoded by LKB1 is not fully understood.

Clinical features include hamartomatous gastrointestinal polyps and mucocutaneous pigmentation. The polyps occur along the gastrointestinal tract, but 70–90% will have polyps within the small bowel. Complications typically occur before the age of 10 years and include intussusception, small bowel obstruction, rectal bleeding and volvulus. Typical freckles will occur on the lips, buccal mucosa, fingers, toes and vulva. There is increased risk of malignancy within the gastrointestinal tract, breast, pancreas, ovary and gall bladder [30]. The lifetime cancer risk is ~10%.

Surveillance with endoscopic polypectomies at 2-year intervals via upper gastrointestinal endoscopy and colonoscopy as recommended. In addition the small bowel can be evaluated by capsule endoscopy.

Mutation screening is available on a research basis only.

MYH polyposis

MYH polyposis is still undergoing definition and should be considered when there are the features of FAP without a demonstrable mutation in the APC gene [24]. Where malignancy has occurred and this diagnosis has been made, endoscopic surveillance of the remaining colon should be undertaken and total colectomy as outlined for FAP should be considered where a genetic diagnosis has been achieved.

Breast/ovarian cancer

Breast cancer is the most common cancer among women in most European countries, with a lifetime risk of ~10%. Ovarian cancer too is a common cancer and has a lifetime risk approaching 1%. About 5% of these cancers are caused by mutations in a cancer predisposition gene, with up to an 85% risk of breast cancer and up to 40% risk of developing ovarian cancer in the presence of such a mutation [7].

BRCA1-related cancers

BRCA1 (MIM No. 113705) was the first gene identified to be associated with an inherited risk of breast and ovarian cancer [3]. The gene is located on chromosome 17q and the usual age of onset of breast cancer is from 35 years of age onwards, although cases can occur much earlier. The ovarian cancer risk is maximal from age 50 years onwards. The risk of contralateral breast cancer after a primary breast malignancy reaches at least 50%.

Two mutations in BRCA1 account for the majority of inherited breast cancer risk within the Ashkenazi Jewish population: 185delAG and 5382insC [13]. The BRCA1 protein is a nuclear protein that mediates protein–protein and protein–DNA interactions. It appears to be involved in the control of mitotic spindles and the segregation of daughter chromosomes while also being involved in DNA repair along with BRCA2 [31].

Affected women should continue having annual mammography on remaining breast tissue and should also have screening for ovarian cancer using transvaginal sonography with CA 125 measurement annually [28].

Screening for ovarian cancer is not a proven modality and prophylactic surgery is a better option once women have completed their families. Recent evidence suggests that prophylactic oophorectomy carried out before the menopause will reduce subsequent breast cancer risk by ~50% [11, 12]. Women too may opt for prophylactic mastectomy, which reduces subsequent breast cancer risk by well over 90% but which poses a more difficult situation for women, having a greater psychological impact.

Screening for mutations is available, but because of the large size of the gene and the scatter of mutations it is a time-consuming process. The presence of a mutation allows for predictive testing of blood relatives.

BRCA2-related cancers

BRCA2 (MIM No. 600185) was the second gene discovered in which mutations predisposed to breast and ovarian cancer [4]. There is also a lifetime risk of male breast cancer of ~6%. While the risk of ovarian cancer is somewhat lower than with BRCA1, the risk of contralateral breast cancer after a primary...
breast malignancy is also ~50%. Overall, the penetrance of mutations may vary between populations and may be lower than that of BRCA1 mutations. The age of onset of malignancy may also be at a slightly later age.

BRCA2 protein functions as a histone acetyl tranferase and is involved in the regulation of transcription with a tumour suppressor function. It interacts with Rad51 in DNA repair and interacts with BRCA1 in pathways that may lead to p53 activity [31–35].

The approach to screening and management is similar to that for BRCA1 [20]. The chromosomal location of BRCA2 is on 13q. Again, the breast cancer risk is from about age 35 years onwards, and ovarian cancer risk peaks from age 50 years onwards.

As with BRCA1 mutation, screening is available but again is time-consuming. The detection of a mutation within a family allows for predictive testing for blood relatives.

Other breast cancer genes

Predisposition to breast cancer through other gene mutations is rare but can be associated with specific clinical features and known syndromes.

Li–Fraumeni syndrome (MIM No. 151623) is associated with germ-line mutations in the TP53 gene on 17p and the CHK2 gene on 22q. The spectrum of tumours includes early onset breast cancer, adrenocortical cancer, bone and soft tissue sarcomas, acute leukaemia, melanoma, germ cell tumours, and gastric, pancreatic and lung carcinoma. When breast cancer presents at a very early age this syndrome should be considered [34]. While mutation testing for TP53 germ line mutations is available, the utility of predictive testing once a mutation is detected is under dispute because of the lack of effective screening and prevention programmes. Testing in childhood is particularly contentious [35].

P-JS (MIM No. 175200), described above in the context of colorectal cancer, has inherited breast cancer risk as a component [30]. Families with HNPCC may also carry increased breast cancer risk.

Cowden disease (MIM No. 158350) is also known as the multiple hamartoma syndrome. The PTEN gene mutated in this syndrome lies on chromosome 10g. PTEN functions through the PI3-kinase/Akt signalling pathway in the control of regulation of cell growth. It is characterised by dermal lesions, notably trichilemmomas, oral mucocutaneous lesions, gastrointestinal polyps, thyroid adenomas and multinodular goitres, breast fibroadenomas, and lipomas. There is an increased incidence of early-onset breast cancer [36] in up to 50% of carriers with a high risk of bilateral disease and an average age of onset in the late 30s. There is also an increased incidence of non-medullary thyroid cancer as well as endometrial cancer. Screening for breast cancer should be offered from age 30 years and screening for thyroid abnormalities is also recommended. Mutation testing for PTEN mutations is not widely available.

Conclusions

As we find ourselves in the era of genomic medicine with an increasing recognition that many diseases arise as the result of genetic predisposition, cancer genetics will become an increasingly important component of cancer care. In cancer medicine in particular, genomics will have a major impact on the care of a common medical condition and this is well-demonstrated when we consider gastrointestinal cancer, breast cancer and ovarian cancer. Environmental factors have a major impact too on the genesis of these common diseases. The gene–environment interaction needs to be considered in our approach to these conditions and our efforts to reduce mortality.

Structuring of services to meet the needs of patients and families in this area requires education of health-care practitioners at all levels through primary care up to those working in specialist cancer centres [37]. Through such education, individual risk can be assessed and determined and people directed towards appropriate services at the appropriate levels.

Health-care professionals will need to understand the various cancer syndromes as well as the genetic basis of predisposition to the common cancers. Such knowledge provides a capacity to prevent disease, to detect it early and to develop new management strategies. In the context of such care many ethical, legal and social issues emerge that have a major impact on the psychological well-being of patients and families who find themselves in need of such care. It is essential that medical oncologists recognise the need for legislation to underpin care in this area, and that they act as advocates for patients and families not only in the provision of services, but also in the enactment of legislation that is supportive and prevents discrimination.

References