

Genetic predisposition to cancer

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Small proportion of cancers develop due to inherited mutations of tumour-suppressor genes, DNA repair genes, and a few recessive genes. Several genes that predispose humans to cancer have been cloned and are used for predictive genetic testing. Interventions such as total colectomy or mastectomy is used for prevention of inherited cancers. However, genetic screening and prophylactic treatments have profound psychosocial effects on patients and families. The first draft of the human genome project has not revealed new genes responsible for common cancers. There is no single technology at present to detect susceptibility due to different genomic abnormalities such as large deletions, rearrangements, base substitutions, small insertions and deletions, amplification, and epigenetic changes like DNA methylation. More laboratory, clinical and ethical research is needed to understand the true extent of genetic predisposition to cancer. We also need to study the social implications of genetic screening in our communities with diverse customs and prejudices so that we can provide socially acceptable treatment strategies.

*Mysteries of creation are like the
darkness of the night. It is great.
Delusions of knowledge are like the
fog in the morning.*

—R. N. Tagore, *Stray Birds*

Background

ALL cancers arise by accumulating structural or functional alteration in cellular deoxyribonucleic acid (DNA)¹. Majority of these alterations of DNA involve mutations of proto-oncogenes, tumour-suppressor genes and DNA repair genes. Around 30 tumour-suppressor genes (recessive oncogenes) and more than 100 dominant oncogenes have been identified². A small proportion of cancers are initiated by germline mutations of these genes, which can be passed on to the offspring. These cancers are termed 'inherited or familial' cancers. This review focuses on genetic predisposition to cancer due to inheritance of defective genes from parents, or as the result of new germline mutations. The inherited predisposition to

cancer has profound medical, social and psychological impact on individuals and families. Fortunately, genetic predisposition to cancer is rare. A recent study of 44,788 pairs of twins revealed that inherited genetic factors make a small contribution to susceptibility to common cancers³.

The study of genetic predisposition to cancer is important. First, the individuals who inherit muted genes are at very high-risk of developing cancer and will benefit from screening and early treatment. Second, close family members of an affected individual are also at high risk of developing the cancer and benefit from screening and early treatment. Third, many inherited cancers have a non-heritable counterpart with a similar genetic pathway⁴⁻⁶. Therefore the inherited cancers offer an opportunity to study the steps involved in the development of sporadic cancer. Fourth, genetic predisposition to cancer may be associated with abnormalities in the control of growth and metabolism of cancerous and non-cancerous cells. Their study may enhance our understanding of the cell growth and development. Finally, patients with inherited cancers attending a cancer family clinic serve as a human model to evaluate the gene-environment interaction in carcinogenesis.

Mechanisms of genetic predisposition to cancer

Genetic susceptibility to cancer is triggered in several ways¹. The most common mechanism involves uncontrolled cell division due to germline mutation of tumour-suppressor genes. This is best illustrated by familial adenomatous polyposis (FAP) syndrome, and the familial retinoblastoma (FRB) syndrome^{5,6}. In patients with FAP one allele of the adenomatous polyposis coli (*APC*) gene is muted in each and every cell in the body⁶⁻⁹. However, not all cells get transformed into cancer cell. It is obvious that several additional steps are essential. The first acquired step involves either a mutation, or the loss of the remaining wild-allele at the *APC* locus. In sporadic colon cancer mutations of both alleles of *APC* genes occur by chance or by exposure to environmental risk factors⁴. In FAP, inheritance of one mutated *APC* allele greatly increases the probability that the remaining wild allele is lost or mutated in some cells. Over periods that range from few years to four decades many colonic cells with germline mutation acquire mutations in the remaining allele. This finally leads to the formation of hundreds to

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thousands of polyps. Cells of some of these polyps acquire mutations in other genes resulting in the development of cancer.

In FRB and sporadic retinoblastoma there is loss of or mutation of both the alleles of the *RB1* gene⁵. Cancer develops only after the loss of both alleles, because *RB1* gene suppresses tumorigenesis⁵. It is a paradox that FRB and FAP have an inheritance pattern that is phenotypically Mendelian dominant, and within the cell the *RB1* and *APC* genes are functionally recessive¹. Because *RB1* or *APC* mutations are functionally recessive, a tumour develops once the target (retinal or colonic cell) acquires somatic mutation of the wild allele. Cancer, unlike inherited metabolic diseases begins in one cell and then proliferates. The number of cells at risk of acquiring the second mutation in FRB and FAP is numerous, such that almost everyone who inherits the recessive mutation will develop cancer^{1,10}. Therefore the clinical pattern of cancer in FRB and FAP resembles a dominant family pedigree (Figure 1).

Several other inherited cancer syndromes such as familial breast ovarian cancer (FBOC), familial neuro-

fibromatosis, Von Hippel–Lindau syndrome, etc. share similar molecular mechanisms. The *RB1* gene is truly recessive since there is no identifiable phenotype with the first germline mutation^{10,1}. However, patients with FAP often have a proliferative abnormality throughout their intestinal epithelium¹². This must be due to expression of the germline *APC* mutation in FAP, since the proliferative abnormality affects almost all crypt cells¹². This marker phenotype effect of *APC* gene mutation implies that the loss of activity of an allele need not be all or nothing. Furthermore, a truncated protein is produced when one *APC* allele is muted. This is also termed ‘dominant negative’, because the mutant allele interferes with the activity of the protein encoded by the wild *APC* allele. This effect is made use of during predictive testing of some inherited cancers like FAP. Phenotypic lesions seen in other inherited cancer syndromes such as neurofibromas of hereditary neurofibromatosis^{13,14}, cysts of Von Hippel–Lindau syndrome¹⁵, and C-cell hyperplasia of multiple neuroendocrine neoplasia (MEN)-2 syndrome^{16,17}, are the result of expression of the inherited mutation. MEN-2 is truly dominant because the germline mutations result in

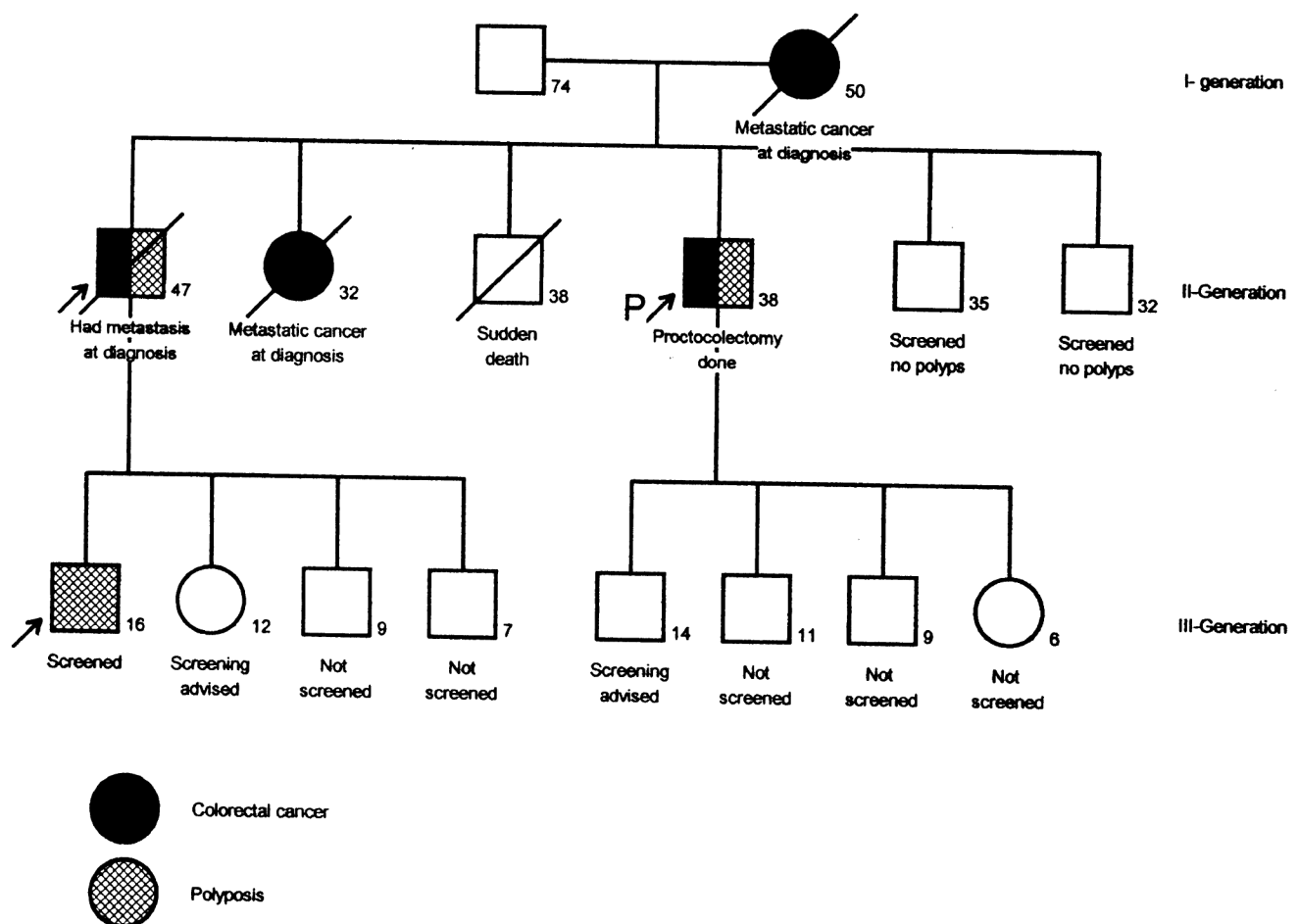


Figure 1. An Indian family with FAP showing the dominant phenotype. Note that FAP can be missed in patients who present with advanced cancer. The compliance for screening sigmoidoscopy in teenaged children is poor in spite of repeated counselling. Patients treated by us are arrow-marked.

activation of the gene product, which is a membrane receptor¹⁸.

Another mechanism for genetic predisposition to cancer involves germline mutations of genes that prevent the repair of acquired mutations of other genes in the carcinogenesis pathway. In hereditary nonpolyposis colorectal cancer (HNPCC) defective DNA mismatch repair (MMR) system prevents repair of DNA alterations¹⁹⁻²⁴. HNPCC is thus caused by germline mutations of any one of the five MMR genes²⁵. The hallmark of this is a genomic instability leading to microsatellite instability in DNA extracted from tumour specimens. Likewise, in Xeroderma pigmentosum, an inherited defect of DNA repair increases the somatic mutation rates in skin cells exposed to ultraviolet light ultimately resulting in the development of skin cancers²⁶. A third and not-so-well studied mechanism involves mutations of genes responsible for catabolism of environmental carcinogens. Families inheriting these defects have a bigger or smaller cancer risk, depending on their ability to metabolize carcinogens or repair exposure-induced DNA damage. For example, glutathione S-transferase M1 (GSTM1) deficiency (null-genotype) is associated with increased lung and head and neck cancer risk²⁷. Lower incidence of some cancers in Indians compared to Chinese or Malays in Singapore may be

attributed to low prevalence of GSTM-1 null genotype in Indians²⁸.

It is important to understand several features unique to inherited cancers while comparing it with inherited metabolic disorders. Most inherited cancers will not manifest in early life and the risk of cancer in gene carriers increases with aging^{16,19}. One hurdle in accurate risk prediction is the lack of age-specific penetrance curves to serve as a guide during counselling¹. Therefore the absence of cancer during first few screening rounds does not exclude subsequent development of cancer. Many unaffected family members at risk tend to become non-compliant with passage of time. Second, within a family, identical mutations may result in the development of different cancers such that screening should target several sites. In HNPCC, some family members develop colon cancer while others may develop cancers of the uterus, stomach, or urogenital tract (Figure 2). Third, mutation of different genes located on different chromosomes can cause same cancers. FOBC is caused by mutations of *BRCA1* and *BRCA2* genes²⁹⁻³⁴, while mutations of five *MMR* genes cause HNPCC syndrome²⁵. Therefore even in well-studied cancer syndromes, we need to search for several genes and as much as 15% to 50% of the genes are still to be identified.

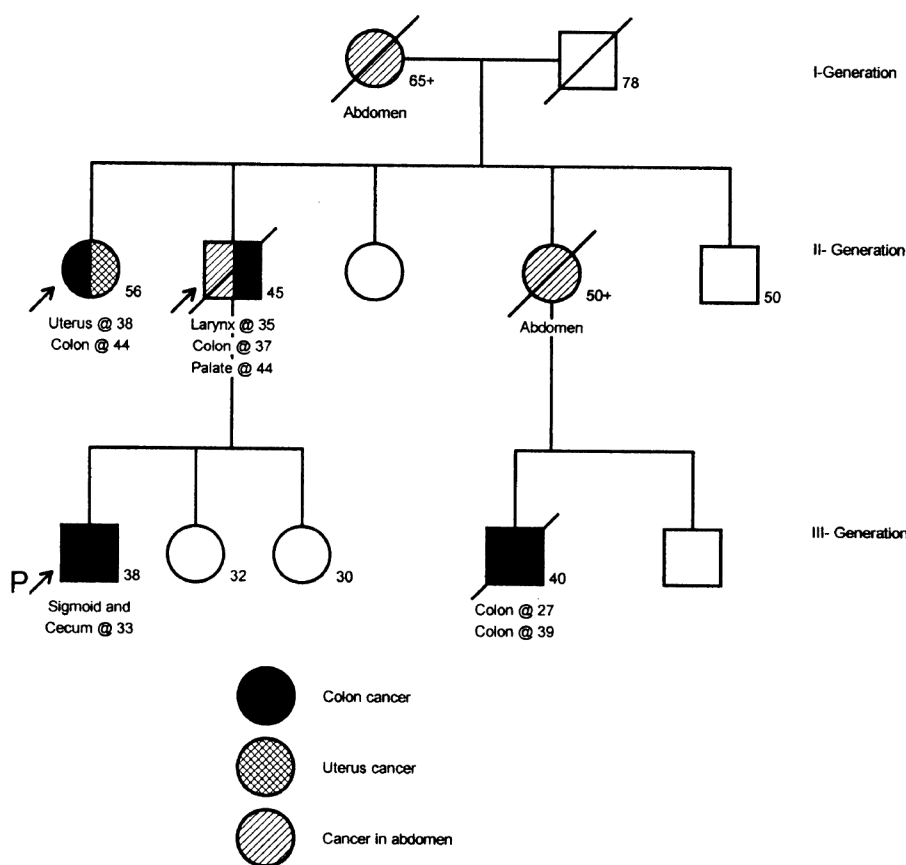


Figure 2. A pedigree of HNPCC showing different cancer sites in affected members. Note that in many older relatives exact site of cancers is unknown. Patients treated by us are arrow-marked.

Phenotypic variations in genetic predisposition to cancer

Mutations in different functional domains of the same gene result in variable loss of activity and this often manifests as phenotypic variation between families (inter-familial)³⁵⁻³⁸. An attenuated variant of FAP is seen in families with mutation at the 5' end of the APC gene³⁵. Such variation may also result from modifying genes, environmental effects, or chance. In FBOC, the predominance of either breast or ovarian cancer may be noted in families because of different mutations in the *BRCA1* gene^{29,36}. Sorting out the influence of these factors in humans is difficult. Phenotypic variation is also seen among members of the same family (intra-familial), and must have another mechanism. Once again environmental factors, modifying genes, background genetic effects and chance are some of the reasons for the intra-familial variation. A hallmark of a strong modifying gene is the clustering of a particular phenotype within nuclear families of larger pedigree. Clinical manifestations of FAP has been seen to vary widely within families³⁹. A study of the neurofibromatosis-1 (NF-1) phenotypes in twins and distant family members concluded that the observed variation in the neuromas and café-au-lait spots could be ascribed to the effects of one or more unlinked genetic modifiers¹³. Several years ago FAP families with ampullary tumours, desmoid tumours, and mandibular osteomas were described as the Gardener's syndrome⁴⁰. Recent studies reveal that the Gardener's phenotype is seen in variable degrees in many FAP families, especially in those with mutations in the region of the APC gene distal to exon 9. Thus, Gardener's syndrome is genetically similar to FAP and variation in the expression is the result of interaction between unknown modifying factors or from the precise nature of the APC gene mutation. The multiple intestinal neoplasm (MIN)-mouse model of FAP is caused due to mutation in the mouse homologue of the APC and sheds some light on gene-gene interaction¹². The number of polyps in the intestine of the MIN-mouse is determined by a single genetic modifier locus MOM (for modifier of MIN) on chromosome 4 (ref. 41).

Inherited cancer syndromes exhibit other forms of variability^{19,42}. Variation in the tumour sites, type and other phenotypic abnormalities is termed expressivity¹⁹. Variability in the age when cancer develops is termed penetrance⁴². A still rare type of intra-familial variability is dependent on the sex of the parent transmitting the defective gene. For example, in dominantly inherited cancer syndromes such as susceptibility to glomus tumour, and rhabdomyosarcoma, the tumour develops only when transmitted through the male germline^{43,44}. Transmission of the gene through females does not express until such time that it is once more transmitted through a male offspring. This phenomenon is called imprinting which suggests that paternally and maternally derived defective

alleles are not equivalent^{43,44}. The molecular mechanism for this is unclear and may be due to differential methylation of genes in the male or female germline. Functionally, imprinting is thought to provide another level of control over the expression of critical genes during embryogenesis. Imprinting is rare in common inherited cancers. These variations offer a real challenge in management of inherited cancers. More clues to the identity of modifier genes will come from animal models, such as the min-mouse model of FAP⁴¹.

Attributable proportion of inherited cancers

The proportion of cancer directly attributed to inherited genes in a population is small. It is generally estimated that about 1% of all cancers are truly inherited. Another 5 to 10% of common cancers that occur in smaller familial clusters are likely to have a genetic predisposition^{1,3}. Many inherited cancers also occur in the absence of an obvious family history. Strong cancer-predisposing genes (e.g. *APC* or *RBI*) arise as new germline mutation or deletions during gametogenesis, without any family history. Weak predisposing genes responsible for common cancers impart a lower relative risk but the attributable proportion may be large^{1,27}. The inherited predisposition, environmental exposure, and the accumulation of a series of stochastic events by chance would interact to different degrees in different populations. The real task is to decide which of these have a sufficiently strong inherited predisposition so that screening and early intervention is practical.

Characteristic clinical features of inherited cancer syndromes

Most well studied inherited cancer syndromes are listed in Table 1. A strong family history is often the first clue. Family history may be lacking in many cases. Lack of knowledge about family history, occurrence of a new germline mutation, or due to non-expression of the gene in the parents (incomplete penetrance) are some reasons. A characteristic phenotypic marker reveals some inherited cancer syndromes. The marker phenotype may be the result of abnormal proliferation of the target tissue (numerous adenomas in FAP or C-cell hyperplasia in MEN2). In others, the marker phenotype are developmental defects in tissues that do not progress to cancer (osteomas of the jaw, CHRPE and abdominal desmoid tumours in FAP⁴⁵, the multiple abdominal cysts in Von Hippel-Lindau syndrome, and ganglioneuromatosis in MEN2-B). Other inherited cancer syndromes, like FRB and HBOC have no characteristic marker phenotype. A heritable variety can still be suspected because of unique features. Cancers in two or more young first-degree relatives, bilateral cancers in one individual, or male breast

cancer provide clues to genetic predisposition^{33,46}. The real difficulty arises when young individuals with one tumour and no family history are evaluated. The majority of these are likely to be non-heritable. Inherited cancer cannot be excluded when a new mutation by chance developed only one tumour. The *RBI* gene has been cloned, and it is possible to detect the germline mutation in doubtful cases with sporadic retinoblastoma¹¹. Inherited nature of cancer is suspected because the genetic predisposition is not to any cancers but to cancers at specific sites. For example in FAP, the cancers develop in rectum, colon, ampulla of Vater, hepatoblastoma, desmoid tumours of the abdominal wall, and thyroid tumours. In syndromes where the genes have not been cloned, the differentiation between a new mutation and non-heritable cancer in the absence of a marker phenotype is difficult.

One of the widely studied inherited cancers is a group associated with adenomatous polyps. The nomenclature between polyposis (FAP) and non-polyposis (HNPCC) is misleading, because the difference is in the number of polyps rather than their absence. Patients with HNPCC do have a few polyps¹⁹. FAP is defined genetically by mutation of the *APC* gene on chromosome 5q21 (refs 8, 9). About 70% of HNPCC families have been shown to have mutations in a family of genes that encode proteins involved in DNA repair. The HNPCC syndrome was formerly distinguished as Lynch type II and I with

increased risks of colorectal, uterine, ovarian, gastric, and breast. The distinction between Lynch types I and II is unclear and both clinical syndromes result from mutations in the same genes¹⁹. Some families carrying the *MSH2* gene mutation have been found to develop the Muir-Torre variant of the familial colon cancer syndrome. Even the distinction between familial polyposis and non-polyposis colorectal cancer is not clear at the genetic level³⁹. Some families with a dominantly inherited colonic cancer (attenuated APC) are associated with fewer numbers of polyps and late presentation and have mutation in the extreme 5' end of the *APC* gene³⁵. There is a wide spectrum of familial predisposition to colorectal cancers that associated with varying number of adenomatous polyps caused by germline mutations of several genes.

Similar situation exists in MEN2 syndrome, where three clinically distinct varieties of cancer result from different mutations of the *RET* oncogene³⁷. As in FAP, 10% of *MEN-2A* gene carriers will test negative to a sensitive biochemical screening test at age of 25, and 40% of gene carriers will not have clinically significant disease by age of 70 (ref. 42). Predicting the penetrance or expression of the predisposing gene in an individual family member is important for clinical management. Unfortunately, this is not possible until the causes of the variation including the modifier genes are better understood.

Table 1. Some inherited syndromes that cause genetic predisposition to cancer

Cancer syndrome	Major cancer	Other cancer	Gene
Hereditary breast/ovarian cancer syndrome	Breast, ovary	Colon, prostate	<i>BRCA1, BRCA2</i>
Cowden syndrome	Breast, thyroid	Others	<i>CD1</i>
Li-Fraumeni syndrome	Bone and soft tissue	Brain, leukemia	<i>TP53</i>
Familial prostrate cancer	Prostate		<i>HPC1</i>
Peutz-Jeghers syndrome	Hamatomas	Ovary, testis, pancreas	<i>STK11</i>
Juvenile polyposis	Colorectal cancer	Pancreas	<i>MADH4</i>
Familial polyposis coli	Colon, rectum	Desmoid, pancreas, liver	<i>APC</i>
Familial gastric cancer	Stomach,	Breast	<i>CDH1</i>
HNPCC syndrome	Colon and rectum	Endometrium, stomach, ovary, urinary, pancreas	<i>MSH2, MSH6, MLH1, PMS1, PMS2</i>
Pancreatic cancer	Pancreas		<i>DPC4</i>
Multiple neuroendocrine-1	Pancreas, pituitary	Parathyroid	<i>MEN1</i>
Multiple neuroendocrine-2	Medullary carcinoma pheochromocytoma	Thyroid, neuromas	<i>RET</i>
Neurofibromatosis-1	Neurofibroma, glioma		<i>NF1</i>
Neurofibromatosis-2	Meningioma	Acoustic and optic neuroma	<i>NF2</i>
Von Hippel-Lindau's disease	Renal cell carcinoma pheochromocytoma	Brain tumours, hemangioma, etc	<i>VHL</i>
Familial retinoblastoma	Retinoblastoma	Breast, sarcoma, lung	<i>RBI</i>
Familial Wilms tumour	Wilms tumour	Hepatoblastoma	<i>WT1</i>
Lung cancer	Small cell lung cancer	Rhabdomyosarcoma	<i>SCLC1</i>
Fanconi's anemia	Leukemia	Esophagus, skin, liver	<i>FAA, FAC</i>
Ataxia telangectasia	Leukemia, lymphoma	Ovary, stomach, brain	<i>ATM</i>
Bloom syndrome	Leukemia	Tongue, colon, esophagus, Wilms tumour	<i>BLM</i>
<i>Xeroderma pigmentosum</i>	Skin cancer	Melanoma, leukemia	Several genes
Cutaneous melanoma	Skin melanoma		<i>CDKN2A</i>
Gorlin syndrome	Basal cell cancer	Brain tumour	<i>PTCH</i>
Familial hemochromatosis	Liver		<i>HPA</i>

Breast cancer is a leading cause of cancer mortality in women. In 1994 two genes that increase the susceptibility to FBOC were identified^{30,32}. Vast majority of families with both young-onset breast cancer and epithelial ovarian cancer result from one of two genes: BRCA1 on chromosome 17q21, or BRCA2 on 13q (refs 30–33). The spectrum of FBOC extends from site-specific breast cancer through breast-ovarian families with each cancer in different proportions to site-specific ovarian cancer. Cancers of the colon, prostate, larynx, and other sites may form part of the BRCA1 and BRCA2 syndromes. BRCA1 mutation is more frequent in families with two or more cases of ovarian cancer. BRCA2 mutation is more common in families with male breast cancer^{33,46}. Some FBOC probably result from genetic predisposition unidentified genes. BRCA1 and BRCA2 help in repairing of DNA following radiation induced breaks and their mutations are thought to disable the repair mechanism leading to more errors in the DNA replication.

The Li-Fraumeni is easily recognizable in its complete form with sarcoma, breast, lung, and adrenal cancers³⁸. Many more borderline families with young-onset breast cancer and a single relative with a sarcoma or a brain tumour raise diagnostic challenges. Approximately 50% of typical Li-Fraumeni pattern families have been shown to have germline mutations at the p53 locus and for many others no predisposing mutation yet identified^{38,47}.

Gene–environment interaction

Many inherited cancers exhibit a complex interaction with the environment. This is best exemplified by the changing pattern of tumour types in large pedigrees. In the Family-G of Warthin with HNPCC, the change in cancer sites has paralleled the spontaneous decline of gastric cancer and the rise of colon cancer in the United States. Geographical variation with excess gastric cancers in HNPCC families from Japan and Korea provides further evidence. In hereditary hemochromatosis prophylactic blood letting to reduce iron overload protects against the development of liver cancer. Patients with Xeroderma pigmentosum have higher frequency of all forms of skin cancer, owing to a genetic defect in DNA repair²⁶. A recent report that topical application of bacterial DNA repair enzymes (T4N5) in a liposomal delivery system to sun-damaged skin of patients with Xeroderma pigmentosum lowered the rate of development of cancer is yet another example of how the environment can be manipulated for control of genetically predisposed cancer²⁶.

Screening and managing cancer families

Inherited cancer syndromes such as FAP, HNPCC, HBOC, FRB, MEN, Von Hippel–Lindau syndrome, and familial melanoma are now amenable to clinical and

genetic screening^{47,48}. Appropriate treatment of those at high-risk helps to reduce morbidity from cancer and restore near normal life expectancy. Screening is cost-effective when simple curative treatments are available⁴⁸. Unfortunately the recognition and screening of most families with inherited cancers is inadequate. Neglect of the family history is the single most important reason. Families can benefit from counseling even when effective screening or treatment is not available. Most individuals with a strong family history overestimate their personal risks and their anxiety can be reduced with good counseling⁴⁹. Because of the rarity of these cancers patients with familial cancers are best managed in a family cancer registry or clinic (Table 2). The details for establishing a family cancer clinic can be found elsewhere⁵⁰. The first step is to determine why the individual showed up at the clinic and what they hope to get. In general, there will be three possibilities depending on the cancer site; do nothing, screening, and prophylactic surgery. Only in a few instances (e.g. familial melanoma – keep out of the sun; breast cancer – consider enrollment in a prevention trial such as the current trial of tamoxifen) is specific advice on primary prevention possible. The uncertainties of screening tests (mammography for breast or trans-vaginal ultrasound for ovarian cancer) and the benefits and drawbacks of prophylactic surgery must be explained in detail so that the patient or family can make their own decision. The implications for children are a major source of concern worldwide. Providing parents with written material and recommendations for the children for later use helps. Great caution and restraint is needed in dealing with other branches of the family at risk. They are best left alone, if they are not in contact with the branch who have sought advice or are unaware of the familial nature of the cancer. Family members who are enthusiastic about information need to be cautioned that other relatives respond differently.

Genetic testing can separate those at high risk from those at usual population risk of cancer. However, genetic

Table 2. Activities in a familial cancer clinic

Obtain detailed family history and construct a pedigree.
Confirm the cancer types in family members.
To estimate individual risks and discuss these with family members.
Counsel clinically affected patients and family members at risk and help them overcome their fears and inhibitions.
Prepare family members at risk for predictive testing.
Discuss suitable options for management of affected and unaffected family members.
Provide information to doctors treating the patients and family members.
To maintain an overview of all branches of the family some of whom may live at some distance.
To ensure that continuity of screening and follow-up is maintained.
To schedule and monitor the screening of relatives at risk regularly.
Maintain a large database of patients with rare familial cancers.
Provide opportunity to family members to participate in clinical and laboratory research.

testing for cancer is not fool proof⁴⁸. Different molecular techniques that are used to test for genetic predisposition to cancer are beyond the scope of this review. Often, more than one method may be necessary during the initial assessment of suspected cancer families. When a specific, predisposing mutation is identified in one family member, the inheritance (or non-inheritance) of this mutation in other family members can be determined. Mutation-based prediction is possible for any familial cancer in which the predisposing gene is known. In practice even when the gene is known, there is a proportion of families (ranging from a few per cent in FAP or MEN2 to majority in NF-1) in whom the specific mutation cannot be identified for various reasons³⁹. It is important to explain these limitations to the families to help them decide about genetic testing. Familial cancers in which the predisposing gene is known but not yet cloned pose even greater responsibility on those attempting a genetic prediction using linkage analysis. The decision for predictive DNA testing is made after careful explanation of all the issues, usually by a clinical geneticist or genetic counselor^{48,49}. In conditions where the genetic risks are clear-cut, DNA testing leads to a straightforward clinical decision. For example, ordering a sigmoidoscopy to look for polyps in children with APC mutations. In other conditions such as familial breast cancer, there are many unresolved problems. Even when a mutation is found, its significance in terms of the risk of cancer at a given age and type of cancer (e.g., breast versus ovarian) may not be clear. Benign polymorphisms may be mistaken for mutations resulting in serious problems. The ultimate interpretation of the genetic information raises ethical issues. A negative result can be reassuring because it implies that the individual has the same risk as the rest of the population. The outcomes of a positive are not straightforward. Some having initially decided to use this information to make a specific decision (e.g. to proceed with prophylactic mastectomy) may back off. Others may have not even considered prophylactic intervention and may be better off with no testing. Given the need for careful counseling and support and for quality control, DNA testing for most familial cancers should only be provided through a properly set-up, clinical genetics service. Over the counter testing as well as those provided by well-intentioned research laboratories without clinical back-up can have severe repercussions in society^{48,51}.

Obstacles in the management of familial cancers in India

Our experience at the Tata Memorial Bowel Cancer Registry over the past five years has revealed that problems in dealing with inherited cancers in India are similar to those in western countries⁵². Failure to take family history is the single most problem that leads to poor

management of these unfortunate patients. Furthermore, there are problems unique to India due to our socio-economic and cultural diversity. Many issues have an ethical angle to it and are summarized in Table 3. For example, how does one obtain a family history of cancer when most patients are not told that they have cancer?. Children and spouses of cancer patients are unable to recall the diagnosis of cancer due to illiteracy or ignorance. The precise cancer sites are unknown and is often labelled as an abdominal mass. Indian marriage practices also cause major ethical dilemmas in the diagnosis and management of inherited cancers. More than 95% of marriages in India are arranged and the details of cancer in young women after marriage are often unknown to her family. We have found that any attempts to obtain history of cancer from female relatives who are married is socially unacceptable for fear of causing marital problems. As for screening we have noted a strong reluctance to screen young and unmarried daughters, since their marriage is the first priority for the elders in the family. To date none of the asymptomatic relatives who showed up for screening to our bowel cancer registry were unmarried women. In general, we have observed that most Indians at high risk of inherited cancer are non-compliant for screening. This is not surprising given the fact that even

Table 3. Anticipated problems while dealing with inherited cancers in India

Problem	Explanation
Lack of taking family history	Because cancer is relatively rare in India, family history is not taken by medical practitioners.
Low life expectancy	High infant and childhood mortality underestimates the true expression of cancer genes.
Small family size	Many Indians now have small families and assessing the true expression of inheritance is difficult.
Lack of knowledge of cancer	Most doctors in India do not inform the patients about cancer. This leads to confusion and or anxiety while obtaining detailed medical history.
Improper medical diagnosis	Cancer in relatives in villages and small towns are often not pathologically confirmed. Medical reports and death certificates of affected relatives are almost always not available.
Superstitions and false beliefs	Patients and families continue to harbour false beliefs even after repeated counseling due to illiteracy and ignorance
Mix-up with benign diseases	Benign diseases like tuberculosis, cholecystitis, dysentery, etc are mistaken for cancer by patients and relatives.
Lack of communication	Fear of cancer and shame of familial disease prevents proper communication among family members.
Gender bias	Women are discriminated against while dealing with cancer screening and cancer treatment.
Lack of informed consent	Subjects often seek a laboratory report even told that the sample is collected purely for research.

well-informed Americans are not interested in genetic screening⁵³. These are real social facts and need to be remembered by researchers and clinicians while managing familial cancers.

The future

Now that we have the first draft of the human genome and significant advances in biotechnology, we have the opportunity for numerous possibilities in genomics. We have to work out as to how genomic information can be applied for identifying cancer-predisposing genes, new diagnostic or screening tools and new therapies. Genomic sequence information can be combined with other databases of information, such as microarray-derived gene expression, SNPs, and even chemical databases for identifying targets and designing compounds as drugs. The hopes for identifying and cloning new genes that predispose to cancer were high. However, the initial outcome of the first draft has been less rewarding². Understanding the mechanisms of carcinogenesis in inherited cancers will offer insights into common sporadic cancers. Post-genomic proteomics will help to understand gene receptor interaction. Studying the distribution of SNP in genes responsible for metabolism of carcinogens will provide useful information on causation of common cancers. However for uncommon inherited cancers the way forward is to establish familial cancer registries and clinics. Only then can we achieve large sample sizes for solving some mysteries of creation and destruction.

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