Hereditary Cancer

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Cancer cases are often clustered in certain families and pedigree analysis indicates that at least 5% of cancer patients have a genetic predisposition to the disease. During the past decade the basic mechanisms for hereditary cancer have been outlined and a large number of the genes involved have been identified. This rapid development has changed the clinical management of cancer families, which now includes surveillance programs directed to early diagnosis of tumors as well as predictive mutation testing to identify gene carriers. This review outlines the molecular basis for hereditary cancer that has become the basis for genetic counseling of cancer families. The organization of clinics for cancer families in Sweden and the clinical implications of surveillance programs and gene testing for cancer predisposition are discussed.

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Cancer is a genetic disease in the sense that the malignant growth pattern is the result of a genetic alteration that can be transferred from one cancer cell to its daughter cells. Usually these mutations are acquired and originate in a somatic cell. However, cancer can be frequent in certain families and in these kindred a germ-line mutation causes a predisposition to cancer which is transferred from one generation to the next as an autosomal dominant trait (Fig. 1). Numerous risk factors for cancer are known but no single factor increases the risk for cancer to the same extent as that caused by a genetic predisposition. Furthermore, carriers of such a genetic predisposition can be identified by very simple measures, and the morbidity and mortality can be reduced considerably in cancer-risk families.

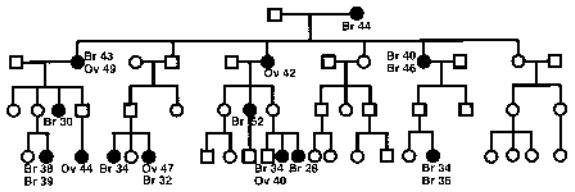

Fig. 1. Pedigree of a typical breast and ovarian cancer family. Circles represent females and squares males. Filled symbols are affected with breast (Br) or ovarian (Ov) cancer with the age of onset indicated. The pedigree illustrates an autosomal dominant mode of inheritance with examples of reduced penetrance—unaffected gene carriers, and varying expression of the disease gene—patients with different organs affected and varying age of onset. Note also several unaffected males who have transmitted the disease gene.

We will outline the basic mechanisms for hereditary cancer. One key question is, of course: How often is cancer caused by a genetic predisposition? By pedigree analysis it is estimated that the proportion of inherited cases of cancer is between 5 and 10% for common tumor types such as colon cancer or breast cancer. However, it is likely that these estimates are low, since there is a considerable rate of new mutations in cancer genes, and these new mutations will not result in a large enough family to be recognized as a cancer family until several generations later. Therefore, even the lowest estimates for the incidence of hereditary cancer show that a genetic predisposition to cancer is a significant health problem (1, 2).

In families prone to cancer, the incidence of the disease increases to an extent that is readily recognized by three very typical clinical signs:

- A family history with multiple affected close relatives (Fig. 1).
- An early age of onset compared to sporadic cases of the same disease.
- Multiple primary tumors.

Any of these findings should remind the doctor that the patient could be member of a cancer family, and that relatives at risk for cancer should be informed and offered different types of follow-up programs.

In the following we first give a very brief outline of the basic mechanisms for inherited diseases, since cancer can be caused either by a chromosomal rearrangement, muta-

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tions in a single gene or by variants in more than one gene often influenced by environmental factors.

Chromosomal abnormalities

Structural chromosome rearrangements are common in malignant diseases, but the abnormality is usually confined to the malignant cell clone and serves to activate an oncogene. Hence, typical cancer-related structural chromosome abnormalities such as the translocation 9;22 in chronic myeloid leukemia (CML), the translocation 11;22 in Ewing's sarcoma or double minutes or homogeneously staining chromosome regions reflecting amplification of the N-*myc* gene in neuroblastoma are not found in constitutional tissue and do not run in families.

However, in rare cases a specific chromosomal translocation may be associated with an increased cancer risk. For example, a few families with balanced translocations involving chromosome 3 and/or 8 associated with renal cell carcinoma have been described, suggesting that the translocation breakpoint alters a cancer-related gene. Furthermore, children with Down syndrome (trisomy 21) have an increased risk of developing leukemia and patients with Turner's syndrome (monosomy X) may have translocated Y-chromosome material, and this causes an increased risk for cancer in abdominal testicular tissue.

In rare cases of retinoblastoma and Wilms' tumor, the child has a constitutional chromosomal deletion of one allele of the *RB1* gene at 13q14 or the *WT1* gene at 11p13 that predisposes to cancer. These rare patients often show different types of malformations and/or mental retardation.

As a general rule, however, constitutional chromosomal abnormalities are rare in cancer families.

Single gene traits

Mutations in single genes can cause diseases that are inherited according to Mendelian laws. Today more than 7000 such disorders have been described and in recent years many of these disease genes have been located and identified. This has lead to an increased knowledge of the molecular mechanisms for many single gene disorders, including several cancer syndromes. The vast majority of the Mendelian disorders are inherited as autosomal dominant, autosomal recessive or X-linked.

Autosomal dominant disorders

The typical cancer family shows this inheritance pattern (see Fig. 1). In autosomal dominant disorders the affected members carry one mutant and one normal (wild-type) allele of the disease gene. The risk for each offspring inheriting the mutation is thus 50%. In typical families half of the children of affected members are affected and the risk to children of unaffected family members is low. However, this general rule is somewhat modified by the fact that the penetrance is reduced for many cancer-causing mutations. This means that the disease may not present at all in some gene carriers while these unaffected persons may transmit the trait and have children with the disease. This is of course very common in families with, for example, breast and ovarian cancer where male gene carriers remain unaffected, or in families with prostate cancer where females do no show any symptoms although they may transmit the disease to their offspring.

One of the most striking features of cancer families is that in one single family, different members may have different types of associated tumors. In breast cancer families a patient could have both breast and ovarian cancer, while other relatives could have breast or ovarian cancer. In some well-known syndromes like Li-Fraumeni syndrome, multiple endocrine neoplasia type 1 and type 2 is associated with tumors in three or more organs.

In most cases the autosomal dominant mode of inheritance reflects mutations in a tumor suppresser gene (see below) and among the best known syndromes with this mode of inheritance are breast cancer, colon cancer, renal cell carcinoma and prostate cancer. However, each type of cancer family may be caused by mutations in one of several different genes. Hence, for breast cancer a number of genes are implicated. Two genes *BRCA1*, *BRCA2* have been isolated and in addition there is at least one or more yet unidentified breast cancer genes. Several other autosomal dominant syndromes also show an increased risk for breast cancer such as Li-Fraumeni syndrome and Cowden's syndrome. Similarly, autosomal dominantly inherited colon cancer can be caused by mutations in the APC gene, resulting in familial adenomatos polyposis. However, a much more common cause of cancer in the great intestine involves deficient DNA mismatch repair, resulting in hereditary non-polyposis colorectal cancer (HNPCC). This syndrome can be caused by a mutation in one of several different genes and is estimated to be the most common cause of intestinal cancer. However, in addition to APC and HNPCC, there are several other rare syndromes that show an increased risk for cancer in the colon.

Molecular analysis of cancer genes have shown that the rate of new mutations is considerable in cancer-related genes. Therefore, although a patient may not have any affected family member, the risk for the offspring can be high.

Autosomal recessive disorders

In autosomal recessive disorders the affected individual have mutations on both alleles of the disease gene and the two parents carry the trait in heterozygous form. Over 1700 such disorders have been described, but each of them is rare, except in inbred populations and consanguineous families where the risk for a couple carrying a mutation in the same gene is greatly increased. Only a few of these rare autosomal recessive disorders have been implicated in can-

cer predisposition. Xeroderma pigmentosum is characterized by a deficient repair of UV-light-induced DNA adducts and an increased risk of skin cancer. Ataxia teleangiectasia patients are deficient in the repair of x-ray-induced damage and prone to various malignancies, primarily of hematological origin. Fanconi's anemia and Bloom's syndrome are also extremely rare cancer-prone disorders associated with additional phenotypes.

X-linked disorders

Over 400 genes have been mapped to the X-chromosome, but only a few of these confer an increased risk for cancer, and in these cases only indirectly. For example, androgen insensitivity caused by mutations in the androgen receptor gene can result in gynecomasty and breast cancer in affected males.

Polygenic-multifactorial disorders

Much of the normal variation in man as well as many common diseases such as coronary heart disease, diabetes, stroke, an so on, are caused by mutations or variants in several different genes combined with environmental and lifestyle factors. This leads to an aggregation of affected family members although the disease does not segregate like a Mendelian disorder. It is likely that the samwe type of mechanisms can also cause an increased risk for cancer in some families and contribute to increased cancer rates in some environments, although we do not know which genes are involved and how the increased risk is generated. However, it is likely that an important fraction of all cancer is caused by polygenic effects.

GENETIC MECHANISMS IN CANCER

From a genetic point of view, malignant diseases can be divided into three main groups depending on the primary event initiating the malignant process (1, 3, 4):

- Growth stimulation through activation of cellular oncogenes.
- Absence of normal growth control because of inactivation of a tumor suppressor gene.
- Accumulation of mutations in critical genes, either through exposure to environmental factors or because of deficient repair of DNA damage.

Activation of cellular oncogenes

Cellular oncogenes play a central rule in many hematological malignancies. For example, the best known cytogenetic abnormality associated with malignancy is the t(9;22) in CML, which is due to the translocation of the c-*ABL* oncogene on chromosome 9 to an aberrant promoter of the *BCR* gene on chromosome 22. Typically, the leukemic cell has one copy of the activated/translocated *ABL-BCR* allele and one normal allele, and this mutation is confined to the malignant cell clone. Hence, the mutation is absent in the germ-line and cannot be inherited. Other oncogene-associated malignancies show similar patterns. Only in a few rare cases have oncogenes been implicated in hereditary cancer (5, 6). The best known example is the *RET* gene, where specific activating mutations cause the autosomal dominant multiple endocrine neoplasia type 2 (MEN2).

Instead, activation of cellular oncogenes is commonly involved in tumor progression, also in cancers that are primarily hereditary.

Inactivation of tumor suppressor genes

A group of genes play a central role in growth and differentiation and is associated with tumor suppression (7, 8). An understanding of these mechanisms springs from studies of the rare childhood eye tumor retinoblastoma, a disease which has served as a model for understanding this group of inherited cancers (9, 10).

Retinoblastoma presents in two forms: a sporadic form which is always unilateral and a familial form that shows an autosomal dominant pattern of inheritance and is characterized by multiple primary tumors, and is therefore usually bilateral. By comparing the age of onset for the sporadic and hereditary forms of the disease, Alfred Knudson postulated that each tumor arises as a result of two independent mutations, each inactivating the two alleles of a single gene. According to the two-mutation model, children with the hereditary form carry one mutation in the germ-line and each retinal cell is therefore predisposed/prepared should a second mutational event in any one retinal cell inactivate or eliminate the remaining normal allele of the retinoblastoma gene. In the sporadic form of the disease, two independent events occur in a somatic cell in the retina. In a child with a germ-line mutation the probability of one additional somatic mutation occurring during any of the several million cell divisions involved in the formation of the retina is high, and therefore each child with a germ-line mutation will develop an average of 3–5 primary tumors. In children who do not carry a germ-line mutation, the probability of two independent somatic mutations occurring in one single retinal cell is extremely low, and therefore only one tumor will develop in 30000 children. Hence, the number of retinoblastoma tumors in a predisposed population is 100000 times higher than that in children who do not carry a germ-line mutation.

The retinoblastoma gene (*RB1*) was the first tumor suppressor gene that was identified and Knudson's model has now been confirmed to its full extent by molecular analysis (11–14). The normal function of the gene product is to participate in the cell cycle regulation through variation in the level of phosphorylation. The gene is expressed in all cells in the body, but inactivating mutations only cause cancer in a limited number of tissues, the retina, bone and to some extent in soft tissue. Molecular analyses have shown that most mutations are 'private', i.e. each

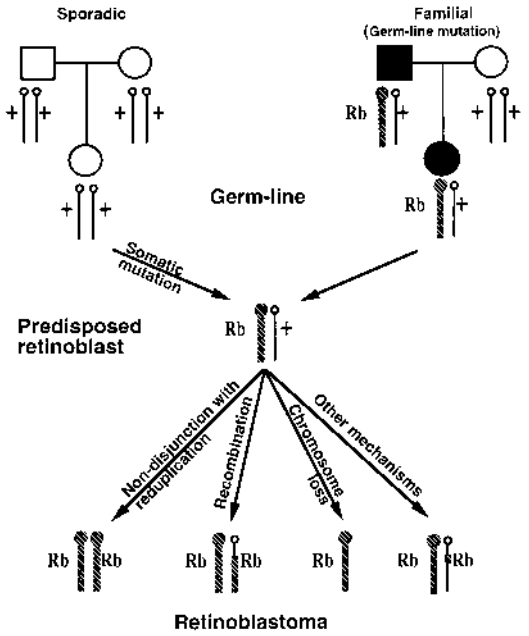

Fig. 2. The two-mutation model for tumor suppressor genes. A first mutation in the retinoblastoma gene (Rb) may be somatic or in the germ-line. A second mutational event eliminates the remaining normal allele (+) by different mechanisms.

family has a unique mutation. The first mutation is usually an inactivation through a small sequence alteration within the gene, interrupting the reading frame of the mRNA, while the second event is often a larger chromosomal event that serves to eliminate the remaining wild-type allele (Fig. 2). At the molecular level the same types of event occur in both the hereditary and sporadic forms of the disease, but in the sporadic form the first of these mutations is somatic, as predicted by Knudson.

The same basic mechanisms that give rise to retinoblastoma have also been found in other more common cancer types. Hence, many different tumor suppresser genes have been identified. Inactivation of these genes is responsible for different hereditary and sporadic cancer forms, including breast and ovarian cancer (the *BRCA1* and *BRCA2* genes), neurofibroma and, basalioma (*PATCH*), melanoma (*CDKN2A*), glioma (*NF1*), meningioma (*NF2*), colon cancer (*APC*), kidney cancer (*WT1*, *VHL* multiple endocrine neoplasia type 1 (*MEN1*), and many more (see Table 1). Since tumor suppressor genes are involved in predisposition to many different common cancer types, this mechanism is a more common cause of inherited cancer than oncogenes and DNA repair defects together, in terms of both the tumor types involved and the number of cancer patients.

DNA repair defects

The living cell has a very delicate system to preserve the integrity of the genetic material. Thirty years ago it was shown that defective DNA repair results in an increased mutation rate, which in turn leads to cancer. Initially, this postulation was based on observations in the rare autosomal recessive disorders, such as xeroderma pigmentosum. However, in 1993 it became evident from analysis of families with HNPCC that defective proofreading of DNA can also lead to cancer (15). The DNA mismatch repair system involves several proteins that recognize the misincorporated base, determines which strand is the correct template, cuts out the incorrect bases, fills in the gap and

Table 1

Familial cancer syndromes associated with gatekeeping TSG

Syndrome	Gene	Main types of tumors
Retinoblastoma	RB1	Retinoblastoma, osteosarcoma
Li-Fraumeni syndrome	TP53	Soft tissue sarcomas, breast cancer, adrenocortical cancer
Familial adenomatous polyposis	APC	Colorectal polyps and cancer
Wilm's Tumor	WT1	Wilm's tumor
von Hippel-Lindau disease	VHL	Renal cell carcinoma, retinal angioma, CNS hemangioblastoma, pheochromocytoma
Gorlin's syndrome	PATCH	Basal cell carcinoma, ovarian fibroma, medulloblastoma
Cowden's syndrome	PTEN/MMAC1	Breast cancer, hamartomas
Tuberous sclerosis type 1	TSC1	Renal angiomyolipomas, rhabdomyoma
Tuberous sclerosis type 2	TSC2	Renal angiomyolipomas, rhabdomyoma
Neurofibromatosis Type 1	NF1	Neurofibroma
Neurofibromatosis Type 2	NF2	Acoustic neuroma, meningioma, schwannoma
Familial breast cancer	BRCA1	Breast cancer, ovarian cancer
	BRCA2	Female/male breast cancer
Juvenile polyposis coli	SMAD4	Gastrointestinal hamartomatous polyps and cancer
Familial gastric cancer	E-CADHERIN	Gastric cancer
Familial melanoma	CDKN2A	Melanoma, exocrine pancreatic carcinoma
Multiple endocrine neoplasia type 1	MEN1	Parathyroid hyperplasia anterior pituitary tumors enteropancreatic tumors
Peutz-Jegher's syndrome	LKB1	Gastrointestinal hamartomoatous polyps and cancer

Modified from Teh et al. (1998) (8).

ligates the DNA-strand. These proteins are coded by at least five different genes in man, all which have been implicated in HNPCC. Of these genes, two are the predominant causes of hereditary colorectal cancer, the *MLH1* and *MSH2* genes. Germ-line mutations in these two genes are found in 50% of HNPCC patients and in 2% of all colon cancer patients.

GENETIC COUNSELING IN CANCER FAMILIES

Members of cancer families are often aware of the risk even before it is evident for the doctor. However, the family members' awareness is often mixed with misconceptions and exaggeration of the actual risk. Therefore, these families often benefit from genetic counseling and different types of surveillance programs directed to reduce morbidity and mortality (16).

The most common cancers—breast cancer and colorectal cancer (CRC)—are also the most common among the familial cases. The risk for breast cancer is increased in close relatives of breast cancer patients and the risk for colon cancer in relatives of colon cancer patients (17). Several inherited syndromes are associated with a very high risk of CRC. The best known of these is familial adenomatous polyposis (FAP) (3), where gene carriers develop hundreds to thousands of adenomatous polyps in the colon, and CRC before 40 years of age. In HNPCC an increased risk for colon cancer is also associated with risk for endometrial cancer, small bowel cancer, renal pelvis cancer, ovary cancer and urinary tract cancer (18). HNPCC is defined by at least three individuals over two generations with CRC, including one patient who was under 50 years of age at diagnosis, the so called 'Amsterdam criteria' (19).

The increased risk for cancer in certain families defines an at-risk population in need of supportive information and surveillance. The surveillance offered in these families is aimed to decrease anxiety in the family members as well as morbidity and mortality attributable to cancer.

Cancer family clinics

In Sweden, genetic counseling is offered to cancer families in specialized clinics. These clinics have been established at the university hospitals and are associated with the Departments of Clinical Genetics in Stockholm, Lund, Umeå, Gothenburg, Uppsala and Linköping. Physicians specialized in clinical genetics, oncology or surgery see the patients together with a nurse trained as genetic counselor. The organization of the units varies somewhat, but there is general agreement that an effort should be made to ensure that the counseling is carried out in a uniform manner, since different members of one family may live in different parts of the country and come in contact with different clinics. Therefore, representatives from all units meet regularly to discuss and plan issues of common interest.

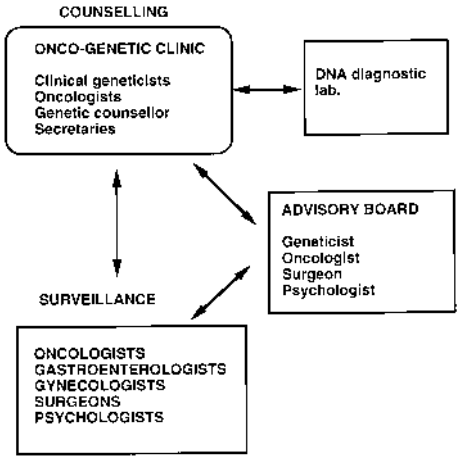

Fig. 3. The organization of the onco-genetic clinic at the Karolinska Hospital.

Presently, national guidelines for the management of families with hereditary cancer are being produced for publication as a 'state-of-the-art' document, supported by the Swedish National Board of Health and Welfare.

Most cases that are referred to the onco-genetic clinics are members of families with an increased risk for breast-, gynecological- and bowel cancer. For the more rare syndromes such as FAP, MEN1 and MEN2, there are special national registries maintained by scientists with a long-standing interest in the particular syndrome. These doctors also provide genetic counseling of these rare disorders. Similarly, there is a national network of 11 centers managing families with hereditary cutaneous melanoma in Sweden, with a central database in Stockholm, at the Karolinska Hospital.

The onco-genetic clinic at the Karolinska Hospital

In 1990 a special clinic devoted to genetic counseling of cancer families was started at the Karolinska Hospital. Today more than 200 families are counseled every year. The organization has gradually developed and now includes a number of other clinics/hospitals in the Stockholm region (Fig. 3).

The clinic only accepts referral patients. The risk estimates and surveillance program for a patient rely on the exact diagnosis of the family members. Therefore, much effort is devoted to verifying the pedigree data with original case histories from the family members' home clinics. This work benefits greatly from the tradition in our country of saving hospital data on patients for many years, since it is otherwise impossible to verify the exact diagnosis of a relative who died years earlier. High-risk individuals are referred to different clinics for surveillance. For most patients with an increased risk for breast cancer, gynecological cancer or gastrointestinal cancer, this is handled by specially trained oncologists, gynecologists and gastroenterologists/surgeons at the Karolinska Hospital, but other

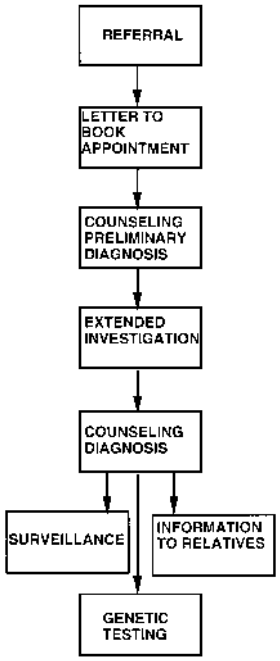

Fig. 4. General outline of patient management at the onco-genetic clinic at the Karolinska Hospital.

hospitals also participate in this program. Patients in need of psychological support can be referred to a psychologist.

Surveillance

Most patients have a family history of breast cancer. For these persons the risk estimate depends on different findings in affected relatives, such as the family history, whether there are associated cancers like ovarian cancer, the age of onset and bilateral disease (20). Risk figures for inherited breast cancer are summarized in Table 2. The surveillance offered for women with increased risk for breast cancer comprises regular check ups with clinical examinations and mammography. Women with increased risk for ovarian cancer are recommended to have regular check-ups with ultrasound. Alternatively, women at risk are offered prophylactic surgery with total mastectomy and primary breast reconstruction and/or prophylactic oophorectomy. Usually, surveillance is recommended at 5–10 years before the earliest age of onset in the family, or at 25 years of age.

Table 2

Cumulative life time (up to 79 years) risk for breast cancer

	Age of onset in affected relative		
	20–29 years (%)	40–49 years (%)	>70 years (%)
Normal risk10%			
One first-degree relative	21	13	9
One second-degree relative	14	10	8
Two first-degree relatives	48	35	11
Mother + aunt	45	34	10
One ovarian + one breast cancer (First-degree relatives)	41	32	17
Three first degree relatives (Familial BRCA)			30–40
Mutation carrier in BRCA1 or BRCA2			50–80

Modified after Claus et al. (1991) (20).

Table 3

Cumulative life time (up to 79 years) risk for colorectal cancer

	Life time risk (%)
Normal risk	5
One first-degree relative	6
One first- and one second-degree relative	8
One first-degree relative below 45 year	10
Two first-degree relatives	17
Three first-degree relatives (hereditary CRC)	50
Both parents	20

Modified after Itoh et al. (1990) (17).

Patients at increased risk for CRC and/or associated cancer such as endometrial cancer are given risk estimates, according to Table 3. Individuals at high risk for CRC are offered regular screening with colonoscopy every two years from an age which depends on the family history. In HNPCC, screening is recommended from age 25. Follow-up studies have shown that regular screening with colonoscopies reduces mortality from CRC in HNPCC patients (21) and in sporadic patients with adenomas (22).

Psychosocial aspects

One important principle for the onco-genetic clinic is that genetic counseling is only offered to those members of cancer families who ask for the information themselves. Therefore the initiative for all contacts must come from the patient. Since patients are always referred to counseling by other doctors, the first contact is through an information letter sent to the patients explaining the purpose of the procedure and asking them to call for an appointment if they want genetic counseling. The first counseling session includes one doctor and one genetic counselor (nurse). The nurse then has further contact with the patient on several occasions during the extended investigation of the family pedigree and the nurse can also offer psychological support, if requested. All persons with an increased risk for cancer are offered a follow-up contact in the clinic within two weeks in order to provide support

should the information cause a crisis in the family. After counseling, patients receive a follow-up letter with a summary of the information. The general outline of the counseling sessions is charted in Fig. 4.

The principle of autonomy

In Sweden, geneticists do not contact family members at risk for a hereditary disease. Instead, the proband is asked to contact family members to share the information. A letter from the counselor can be used for this purpose, but usually the relatives are encouraged to contact an onco-genetic clinic for counseling and surveillance.

Predictive testing in cancer families

In cancer families there is often a demand for predictive laboratory testing of unaffected family members. The rationale for these tests is of course that gene carriers can be offered different types of preventive measures to reduce morbidity and mortality. In this context we would like to point out that these tests are limited by the fact that, with very few exceptions, each family carries a private mutation. Hence, in order to perform a predictive test on a relative, the exact nature of the mutation segregating in the family must be determined.

Predictive testing for hereditary cancer has become an established part of modern healthcare. However, unlike other laboratory tests, predictive testing is complicated genetically, technically, and ethically (23). The testing is performed on normal, healthy individuals and the test results may cause a person to undergo extensive screening programs or to have organs surgically removed in order to avoid cancer. If the test result shows that the person does not carry a cancer predisposition, the person at risk may be excluded from such measures. Hence, misinterpretation of test results can be potentially life threatening and therefore testing must always be performed on strict indications and results must be given to the 'patient' by physicians with a profound knowledge of the genetics of the disease tested for.

This first analysis requires an exact determination of the DNA sequence variant of an affected family member. This often involves several problems. Often the family may be a very large cancer family, but there are no living relatives with the disease available. Another common problem is that the disease gene is large and complicated to study in detail, and in addition mutations in more than one gene may cause the same type of inherited cancer. The last-mentioned problems are true for both colon and breast cancer. Last, but not least is that detailed DNA sequence analysis often fails to produce a conclusive result. Some of the sequence variants found are rare but do not appear to affect the gene function. In other instances no mutation can be detected, either because the mutation is hidden in an intron, or simply because the wrong gene is being studied.

Taken together, predictive testing of cancer is complicated and should be confined to specialists with sufficient knowledge of both the mutational spectrum and the genetics of the disease. However, in those cases where laboratory testing is conclusive, this is important for the family. When the exact mutation has been detected in a particular family, subsequent testing is often relatively easy and can be limited to one single mutation. In some populations low penetrance founder mutations for breast cancer or colon cancer have been detected in several cancer patients, previously not known to be related. In such instances, screening for one or a few common mutations can be rewarding. However, if this particular mutation has not been found in a close relative, a negative result is inconclusive and should never lead to altered management of at-risk individuals.

Clinical implications of mutations in cancer genes

The first breast cancer gene, *BRCA1* was identified in 1994 (24) and this gene was shown to cause breast cancer but also ovarian cancer in families. Many different mutations have been identified in this gene and mutation frequencies as well as founder mutations vary between populations. A second breast cancer gene, *BRCA2*, was identified a year later. This gene causes primarily breast cancer, including breast cancer in males (25).

HNPCC is caused by mutations in genes involved in DNA mismatch repair (15). Two such genes, *MLH1* and *MSH2* are the most important and show high frequencies of mutations in familial colorectal cancer. About 50% of HNPCC cases carry mutations in one of these two genes. The HNPCC-associated tumors have a very high frequency of somatic mutations in short mono- and dinucleotide repeats (26). This phenomenon is called microsatellite instability (MSI), and is defined by somatic mutations in at least two of five specific repeat loci tested.

In order to assess which patients would benefit from mutation screening for the known cancer genes, we performed a number of mutation screening studies, looking for mutations in various breast- and colon cancer genes. We found that patients from families with breast- and ovarian cancer frequently have mutations in the *BRCA1*, while in families with only breast cancer *BRCA1* mutations are rare (27). In a study of *BRCA2* we found a very low frequency of mutations in both breast cancer and breast–ovarian cancer families (28). If all families with breast cancer only are screened, constitutional mutations in BRCA1 or *BRCA2* will be found in less than 10%. Therefore, mutation screening for breast cancer genes is restricted to families with:

- Breast–ovarian cancer syndrome.
- Hereditary premenopausal breast cancer.
- Two cases of breast/ovarian cancer if one was affected before 40 years of age.

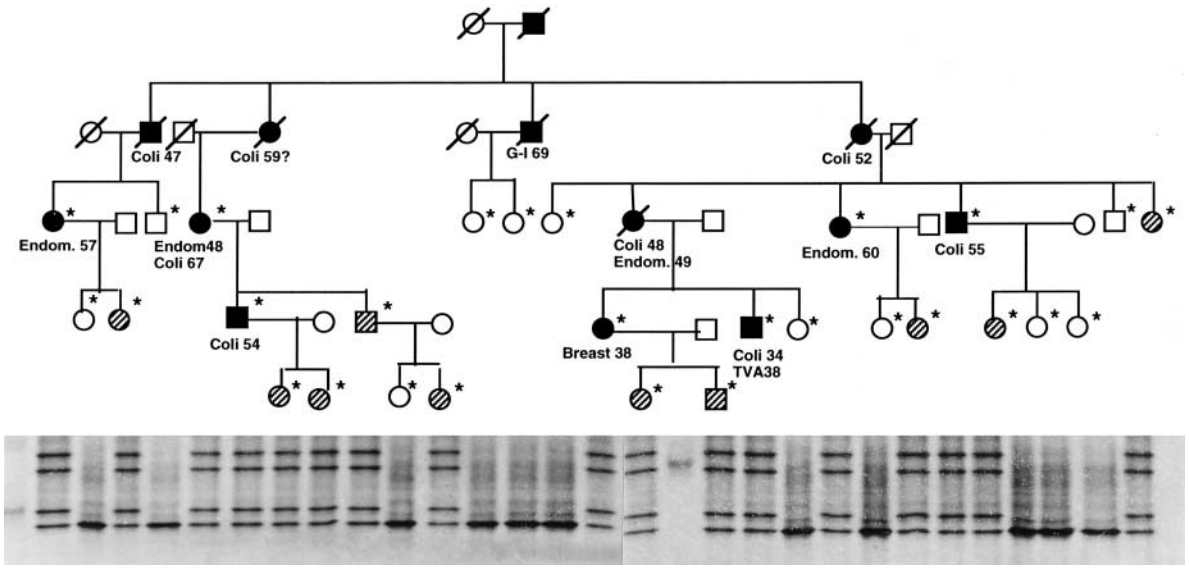

Fig. 5. A family with hereditary non-polyposis colorectal cancer (HNPCC) tested for a mutation in the *MLH1* gene by PCR and denaturing gradient gel electrophoresis. Pedigree symbols: filled—affected individuals; open—unaffected; and dashed—unaffected gene carriers. The gel below the pedigree shows the DNA base sequence alteration. The normal sequence generates one band and the base substitution four (heteroduplex) bands in gene carriers. * indicates patients whose DNA analyses are shown below the pedigree.

– One case of breast/ovarian cancer presenting before 35 years of age.

Screening for mutations in DNA mismatch repair in our population showed mutations in 50% of the HNPCC families and 20% in other patients at risk for CRC that do not fulfil the strict criteria for this syndrome. In general, families with colon cancer and endometrial cancer, or at least one case of very early onset CRC demonstrate a high frequency of mutations. However, the finding of MSI in a tumor from a CRC patient with any family history of CRC or very early onset is the best predictor of a mutation in one of the DNA mismatch repair genes (unpublished data).

Clinical implications of predictive testing in cancer families

If the disease-causing mutation has been found in a family, it is then relatively easy to identify gene carriers with a very high risk of cancer and, equally important, non-carriers who are no longer at risk and do not need surveillance. When a mutation is found, the family is offered a predictive laboratory (Fig. 5). The test procedure involves a first visit for information about the disease, present risk, possible outcome of the test, surveillance available for high-risk individuals, as well as information on possible socioeconomic consequences regarding future employment and life and health insurance. We then require that the family member at risk waits for at least four weeks after counseling. The family member must then take an initiative to have a blood sample taken for the test. This allows the person sufficient time to make a well thought through decision and reduces the risk that the person later regrets having consented to the test. When the test result is available, a letter will be sent requesting the patient to make a new appointment in order to receive the result at the clinic.

Women who consider prophylactic surgery are referred to a surgeon or gynecologist. All patients considering surgery are offered a visit to a psychologist involved in the program. The overall handling time for a patient under consideration for surgery is about one year. To optimize the advice and decisions an advisory board, including all professional categories connected with these patients, is always consulted (oncologists, geneticists, counselors, nurses, psychologist and surgeons) for any patient considered for surgery.

Genetic counseling in cancer families is a recent development. The patients are offered counseling, presymptomatic testing when possible, and surveillance. There is good evidence that the patients benefit from surveillance and that this reduces anxiety, morbidity and mortality caused by cancer. However, these patients need special consideration and the counseling and follow-up require a staff that is specially trained to obtain the best result from the genetic counseling as a new service in modern medicine.

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