Inherited cancer syndromes

Both adult and paediatric cancers are associated in approximately 10% of cases with a hereditary component.

Epidemiological and genetic studies have identified the presence of highly penetrant cancer gene families. Essential clinical evidence for establishing the presence of a familial cancer include the following:

1. Development of tumour in an individual in a family at a much younger age, (less than 40), than that normally observed for the general population.

2. The development of cancers in paired organs, such as bilateral breast cancer, or bilateral renal cancer, or multiple cancer sites in one organ.

3. Several first degree or secondary relatives with the same cancer.

4. Several first-degree relatives with a related cancer, for example, breast, ovarian and endometrial cancer, are related cancers.

5. Two family members with the same rare cancer.

6. The presentation of cancer in an unusual sex, for example, breast cancer in a male, in conjunction with a related breast cancer in a related female.

Even before the advent of modern molecular biology, it was clear that some cancers appeared to occur more frequently in certain families. Familial aggregation has been found in virtually every type of human cancer, including carcinomas, sarcomas, leukemias and brain tumours.

Some of these familial cancers may relate to shared exposure to specific carcinogens, but in some cases it is due to a genetic predisposition. A person who has a parent or sibling who developed cancer at a young age, has approximately twice the risk of developing the same cancer.

Inherited cancer syndromes (cont)

The identification of inherited cancer susceptibility genes is in its infancy. Single gene defects associated with a cancer development, account for less than 10% of cancers.

Cancer susceptibility syndromes are hetrogeneous, that is there are a number of genes that when abnormal can lead to a similar phenotype (clinical expression of diseases).

The interpretation of pedigrees for common cancers must take into account that these are common diseases and may occur in the absence of a specific inherited mutation sporadic cancer. For many common cancers, such as breast or colon cancer, sporadic cases may be indistinguishable clinically from inherited cases, this is known as “phenocopy”.

Sporadic cancers arise from acquired somatic mutations and not from an inherited genetic predisposition (germ line mutation). Somatic mutations occur in non-gamete body cells. After mitosis, these mutations are inherited by the daughter cells. Germline mutations arise in cells that give rise to gametes and therefore will be inherited not only by daughter cells but also passed on to new organisms at fertilization.

Cancer has both genetic and environmental influences that regulate the expression of a particular phenotype. The clinical presentation or phenotype associated with specific inherited cancer syndrome may be relevant to that specific gene.

In considering cancer prone families, one has to take into account the penetrance of the gene defect, and the sex influence.

For example, the **penetrance** of the gene defect will predict whether all or only some of the patients with this gene defect will eventually develop this disease. The penetrance represents the percentage of individuals with a specific gene defect who will express the phenotype i.e., get the disease.

Inherited cancer syndromes (cont)

The identification of genes associated with familial cancer syndromes has enabled the development of molecular diagnostic screening tests, which can predict the number of affected individuals in one family i.e., direct cancer surveillance for those individuals who may be at risk of the disease.

Screening requirements for inherited cancer

Genetic screening tests are gradually being developed to identify cancer prone families. Critical features essential for such a genetic test including the following:

1. Any test designed to detect a malignant or pre-malignant condition at a pre-symptomatic age should have high sensitivity and specificity. This means the test should be able to detect all abnormalities and have a low false positive rate.

2. The treatment of persons detected by screening should improve the long term prognosis for the patient.

3. The benefit of early detection should outweigh any potential harm from the screening test.

4. The test should be non-invasive.

5. Pre-screening counselling should be available.

6. Prevention or early detection is the ultimate goal in the management of any patient with a familial cancer syndrome. Screening includes gene testing and looking for early clinical evidence of the phenotype whether it is colonic polyps or breast lumps. The benefits of the screening long-term need to weighed against the cost, both physical and emotional, for the patient.

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Screening requirements for inherited cancer (cont)

There are potential benefits and risks associated with either positive or negative testing for mutations of specific genes associated with hereditary cancer syndrome. Should the test prove positive, potential benefits include identification of a specific mutated gene locus and increased motivation for the prevention and surveillance of specific cancer.

This may result in a lowered threshold for biopsy of a suspicious lesion and early detection of primary tumours.

Potential risks in the identification of a positive mutation in a cancer prone family are that the individual at risk may be discriminated in terms of insurance and/or employment.

Identification of a cancer-prone family, or individuals, may result in disruption of family relationships and psychosocial issues. In terms of the clinical management it may result in over biopsying a potential affected individual. Should the genetic screen prove negative i.e., the mutation is ruled out in a known mutation-carrying family, the potential benefit will include reduction in anxiety in that particular individual. However, potential risks of a negative screen include survivor guilt, resulting in destruction of family relationships, and in addition a false sense of security including abandonment of cancer prevention and surveillance for strategies.

One of the significant issues to be addressed upon the detection of a positive mutation in a cancer-prone family is that treating physicians should be able to offer the patient some clear guidelines in terms of improved management of that particular cancer.

Screening requirements for inherited cancer (cont)

Clear guidelines may be available for patients with cancer gene mutation with 100% penetrance, such as certain colo-rectal cancers, however, it is less clear what the management should be in breast cancer prone families with inherited BCRA-1 mutations in which not all members of the family will get breast cancer within the lifetime of the patient.

In addition the treatment strategies may not clearly defined, or offer the potential for complete cure. These issues should be discussed with family members prior to the commencement of genetic screening.

Breast and ovarian cancer syndromes

Breast cancer is the most common malignancy in women and comprises 18% of all female cancers.

It is the single most common cause of death in woman in the age group 40-50. Approximately 1 in 10 woman will develop breast cancer during their lifetime. Between 5 and 10% of female breast cancers may be attributed to highly penetrant single gene defects.

In addition to familial predisposition towards breast cancer due to an inherited genetic defect, there are other established risk factors for breast cancer which include geographical location, age at menarche, age at menopause, age of first full pregnancy, evidence of previous benign disease, carcinoma in the other breast, diet, such high intake of such fat, and exposure to ionising radiation, in particular abnormal exposure in young females, after the age of 10, may place these individuals in a high risk group.

Breast and ovarian cancer syndromes (cont)

The genes known to be involved in familial breast cancer (BRCA1 and BRCA2) account for only about 20% of the familial risk. Most of the genetic variants that contribute to the risk of developing sporadic breast cancer are unknown. Many of these may interact with environmental agents, such as radiation, that are known from epidemiological and experimental studies to cause cancer.

Familial Breast Cancer - Criteria for risk

A woman who has one or first degree relative with bilateral breast cancer, or breast and ovarian cancer, or one first degree relative with breast cancer diagnosed under the age of 40 years, or one first degree relative with breast cancer diagnosed at any age, or two first or second degree relatives with breast cancer diagnosed under the age of 60 years, or ovarian cancer at any age on the same side of the family, or three first or second degree relatives with breast and ovarian cancer on the same side of the family, are at substantial increased risk of developing breast cancer.

A first-degree relative is a mother, sister or daughter; a second-degree female relative is a grandmother, granddaughter, aunt or niece.

In addition to female breast cancer, males may in breast cancer prone families also develop breast cancer. Prostrate cancer also appears to have an increased incidence in these breast cancer prone families.

Many families affected by breast cancer also show an excess of ovarian cancers, colon, prostate and other cancers, attributable to the same inherited mutation.

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Familial Breast Cancer - Criteria for risk (cont)

Most women, who have an inherited genetic mutation in a breast cancer associated gene defect, will develop breast cancer before the age of 65 and commonly before the age of 40. In inherited forms of breast cancer in which the BRCA-1 gene is mutated 51% of affected individuals will develop breast cancer by the age of 50, compared to the general population in which the lifetime risk of developing sporadic breast cancer is 11%.

28% of affected individuals with mutations in the BRCA2 gene will develop breast cancer by the age of 50. The lifetime risk of breast cancer in BRCA-1 and BRCA2 affected individuals is between 83-88%, up to the age of 70.

In addition the lifetime risk of ovarian cancer in this group of patients with inherited breast and ovarian cancer syndrome is between 16 and 60%.

Features that enable the physician to identify an increased likelihood of an individual having a BRCA-1 mutation include:

1. Multiple cases of early onset breast cancer in the same family.

2. Ovarian cancer with a family history of breast or ovarian cancer in the same woman.

3. Breast and ovarian cancer in the same woman.

4. Bilateral breast cancer.

5. Ashkenazi Jewish heritage.

6. Male breast cancer.

Molecular determinants – BRCA-1

BRCA-1 is an inherited breast cancer susceptibility gene, which is only rarely mutated in sporadic breast cancer syndrome but frequently mutated in inherited breast cancer syndromes.

Individuals with mutations in this gene often present at an early age onset, often with pre-menopausal breast tumours and/or ovarian cancers, as part of a BRCA-1 linked breast cancer family.

Molecular determinants – BRCA-1 (cont)

These breast cancers are often associated with an aggressive tumour phenotype and may be estrogen receptor negative (i.e. insensitive to hormonal manipulation therapies).

The BRCA-1 gene encodes for a very large protein.

Over 500 different mutations in the BRCA-1 gene have been reported. Many of these mutations are only observed in one particular family.

The majority of mutations result in a truncated protein. Therefore screening to detect mutations for the first time in the affected individual family is technically extremely demanding.

However, certain mutations occur at high frequency in specific defined populations, for example, some 20% of Jewish women of Ashkenazi type carry the BRCA-1 mutation, placing this population at high risk in developing cancer.

BRCA-1 gene function

The loss of function type mutations observed in these particular families with a hereditary predisposition to breast cancer suggests that BRCA-1 is a tumour suppressor gene.

It is probable that BRCA-1 is involved in regulating proliferation and differentiation in many tissues in response to ovarian/hormone stimulation. The gene encodes for a nuclear phospho protein of 220 kilodaltons, which probably plays a role in the maintenance of DNA integrity.

Both BRCA-1 and BRCA2 form a complex with RAD51, a protein involved in meiotic recombination and DNA damage response in rapidly cycling cells. Both BRCA-1 and BRCA2 contribute to the regulation of homologous recombination in DNA repair and embryonic proliferation. The precise function of BRCA-1 awaits further investigation.

BRCA-1 and BRCA2 mutations are the most common causes of autosomal dominant highly penetrant breast cancer susceptibility syndromes.

Molecular determinants – BRCA-1 (cont)

Testing for BRCA-1 became available in 1996, however, there are certain problems associated with genetic testing for both BRCA-1 and BRCA2. These include that only 50% of the family will have the mutation and many mutations (<500) have been reported associated with BRCA-1, so there is no simple test to screen for the specific mutation. In some instances, sequencing the entire gene is required, which is technically demanding.

When testing for genetic mutations in an affected family the optimal testing strategy is to initiate testing on the youngest affected individual, however, in many affected family members, no one may be alive to test. In this case one may proceed, but only in a context of thorough genetic counselling explaining to the family the limitations and benefits of genetic testing, i.e., the genetic should result in an early identification of an at-risk individual and therefore provide early detection and a survival advantage to the patient. Unless there is a highly suggestive family history, cancer susceptibility to testing is not considered appropriate for screening unaffected individuals, except specific ethnic groups where BRCA-1 mutations are more common.

Requirements for screening persons at risk

1. The test should detect a malignant or pre-malignant condition at pre-symptomatic age with high sensitivity and specificity.

2. The treatment of persons detected by screening should result in improvement in their long-term prognosis.

3. The benefit of early detection should outweigh any potential harm from the screening test.

4. The test should be non-invasive.

5. Pre-screening counselling should be available.