

CANCER: the significance of family history

Information for health professionals

Approximately 20% of cancer patients have a positive family history of cancer which may be due to:

- ❖ coincidence
- ❖ common environmental and lifestyle factors
- ❖ genetic factors

Significant developments in cancer genetics have occurred in the last decade. Some of the genes involved in the **inherited susceptibility (or predisposition)** to common cancers have been identified. The result is an improved understanding of cancer risk based on family history of the disease.

Most cancers result from the accumulation of genetic changes (mutations) in cells over a lifetime. However, **only around 5% of certain cancers are considered to involve the inheritance of a genetic predisposition.**

EVALUATING FAMILY HISTORY

Individuals reporting a family history of cancer often want to know the degree to which their family history impacts on their own risk of developing cancer.

The best way to identify whether an individual is likely to have inherited a genetic predisposition to cancer is through careful evaluation of an extended family history. This history needs to include as many blood relatives as possible on both sides of the family, both with and without cancer. The details of each reported cancer site and the age at diagnosis should be verified if possible.

Patterns of cancer in the family history can be used to categorise the history as "familial" or may suggest the presence of a specific hereditary cancer syndrome.

Most often, the history will suggest the cancer is familial. This means the individual's risk may be slightly above average or moderately increased and warrant increased screening. In these cases, current screening and management guidelines for the type of cancer in the family (eg bowel, breast, ovarian) should be followed.

Less often, a family history may indicate the likelihood of an **inherited predisposition to cancer** (or hereditary cancer syndrome). These family histories tend to have certain features in common (see next column).

WHEN TO SUSPECT AN INHERITED PREDISPOSITION TO CANCER

The likelihood of an inherited predisposition to cancer should be considered in an individual (with or without cancer) with a family history of the following:

A) Common cancers

- ❖ three or more cancers of the same type or related types in close blood relatives on the same side of the family [eg breast cancer, breast and/or ovarian cancer, bowel cancer, bowel and/or uterine cancer, prostate cancer, melanoma]
- or
- ❖ two cancers of the same type or related types in close blood relatives on the same side of the family, at least one diagnosed before age 50.
- or
- ❖ an immediate relative (parent, sibling) with one of the common "adult" cancers (eg breast, bowel) diagnosed below the age of 40.

B) Two or more less common cancers in the same individual or in close blood relatives (eg brain, leukaemia or sarcoma)

C) Cancer in the context of an associated genetic syndrome (for example):

- ❖ glioma in neurofibromatosis type 1
- ❖ melanoma with dysplastic naevi
- ❖ renal cancer with retinal angiomas (Von Hippel Lindau)
- ❖ bilateral retinoblastoma

FAMILY CANCER CLINICS AND GENETIC COUNSELLING SERVICES

Individuals whose family history indicates the likelihood of an inherited predisposition to cancer can be referred to a family cancer clinic or genetics service for risk assessment, genetic counselling, genetic testing (where appropriate), identification of other “at risk” relatives and advice about prevention, cancer screening and early detection.

To be seen at a family cancer clinic or genetic counselling service, patients need to have a referral from a medical practitioner. All patients will be referred back to the referring GP/specialist for further management and follow-up.

GENETIC TESTING IN CANCER FAMILIES

Genetic testing is moving from research laboratories to clinical service. In order to identify if a mutation is present in a cancer predisposition gene, a person who has (or had) cancer to be tested first. If a mutation is identified, then blood relatives can be offered testing.

Genetic testing should only be offered with appropriate pre and post-test counselling. This counselling involves discussing the limitations, potential benefits and possible disadvantages of testing. Individuals should be prepared for the event of a positive, negative or inconclusive genetic test result.

A special consent form is used by family cancer clinics and genetics services to cover most of these issues. Follow-up and support after genetic testing are essential together with a specific plan for prevention, screening and early detection.

Types of cancer that can be due to an inherited gene fault

It is thought that about 5% of the common cancers in Australia are attributable to an inherited gene fault. These types of cancer include:

1. bowel cancer [including familial adenomatous polyposis (FAP) and hereditary non polyposis colorectal cancer (HNPCC)]
2. breast and ovarian cancer
3. melanoma

There are also some rarer inherited cancer predisposition syndromes such as Li Fraumeni syndrome, Von Hippel Lindau disease and multiple endocrine neoplasia which may involve more than one type of cancer.

1. Bowel cancer

Familial adenomatous polyposis (FAP)

FAP is a dominantly inherited condition due to a mutation in a gene called the *APC* gene. FAP accounts for about 0.5% of all bowel cancer. Individuals with a mutated *APC* gene develop hundreds of colorectal adenomatous polyps which generally appear in the teenage years. If left untreated, one or more of these adenomas will progress to cancer, often at a relatively early age. Manifestations outside the bowel may occur such as upper GI cancer - especially of the duodenum, desmoid tumours and osteomas.

A diagnosis of FAP in an adult means that each of their children is at 50% risk of having inherited the *APC* gene mutation and therefore developing FAP. Other blood relatives may also be “at risk”.

Genetic testing can now be used to identify the *APC* gene mutation in an affected individual. Once the mutation is identified, “at risk” blood relatives can be tested to determine whether they have inherited the same mutation (predictive genetic testing).

Only the individuals who have inherited the mutation will need screening by sigmoidoscopy (from the early teenage years or sometimes earlier) and preventive measures such as bowel surgery.

Importantly, those without the mutation still have the general population risk of getting some form of bowel cancer. The general population risk before the age of 75 years is about 1 in 18 for men and 1 in 26 for women.

Hereditary Non Polyposis Colorectal Cancer (HNPCC)

HNPCC is a dominantly inherited condition caused by a mutation in one of the DNA mismatch repair (MMR) genes. It accounts for 1 to 4% of all bowel cancers. Families with HNPCC have a strong history of colorectal cancer, characterised by: early age of onset, a tendency for cancer to occur higher up the bowel and multiple primary cancers.

Cancers occurring outside the colon may also be a feature of HNPCC. The most common of these is endometrial cancer, but the syndrome also includes cancers of the ovary, stomach, small bowel, upper renal tract, brain and sometimes other cancers.

As with FAP, once a causative mutation is identified in an affected individual, other family members can be offered predictive genetic testing, and those found to carry the high risk gene mutation can be targeted for cancer screening and prevention strategies. Those without the causative family mutation still have the general population risk of getting some form of bowel cancer.

2. Breast and ovarian cancer

Between 1% and 5% of all breast and ovarian cancers (and a higher proportion of early onset cases) are thought to involve an inherited mutation in a specific predisposing gene (such as *BRCA1* or *BRCA2*).

Approximately 1 in 1,000 men and women are estimated to carry a mutation in such a gene, although the proportion is higher (about 1 in 100) in those of Ashkenazi Jewish descent.

Mutations in *BRCA1* and *BRCA2* give females a 40 - 80% lifetime risk of breast cancer and a 10 - 60% lifetime risk of ovarian cancer. There is also evidence to suggest a slightly increased risk of prostate cancer in males who are carriers of these mutations. *BRCA2* mutations have been associated with male breast cancer.

Management options for high risk women include lifestyle changes, careful individualised cancer screening, participation in the Tamoxifen Prevention Trial and consideration of preventive surgery.

Genetic testing may help to clarify the risk for an individual but the causative mutation must first be identified in an affected blood relative. Mutation detection is time consuming and expensive and current methods **cannot** detect all mutations. However, if a mutation is found, predictive testing of unaffected blood relatives is relatively simple.

3. Melanoma

Family history is an important risk factor for melanoma. Individuals with one affected first degree relative have a 2-3 fold increased risk of developing the disease. Some 5% of all melanoma is thought to be due to inherited mutations in melanoma related genes. The genes involved include *CDKN2A* and *CDK4*.

Melanoma families show a dominant pattern of inheritance, early age of onset, multiple primary melanomas and sometimes the presence of multiple atypical (dysplastic) naevi. Genetic testing of such families is usually undertaken in a research setting. Where a causative mutation is defined, predictive genetic testing for "at risk" family members will be available.

4. Rare inherited cancer predisposition syndromes

These include the Li-Fraumeni syndrome, Von Hippel-Lindau disease, multiple endocrine neoplasia, hereditary retinoblastoma and others. Careful evaluation of the family history of cancer will help to identify such families, who may benefit from genetic counselling, risk assessment, genetic testing where available and specialised cancer screening/prevention.

CONTACT NUMBERS FOR FAMILY CANCER CLINICS IN NSW

Hunter Genetics (Newcastle/Northcoast): Ph (02) 4985 3132	Royal Prince Alfred Hospital, Camperdown: Ph (02) 9515 5080
Liverpool Hospital, Liverpool: Ph (02) 9828 4665	St George Hospital, Kogarah: Ph (02) 9350 2315
Nepean Hospital, Penrith: Ph (02) 9845 5079 (for appointments)	St Vincents Hospital, Darlinghurst: Ph (02) 8382 3395
Prince of Wales Hospital, Randwick: Ph (02) 9382 2609	Westmead Hospital, Westmead: Ph (02) 9845 5079

If you are in a country area, contact the NSW Cancer Council's Cancer Helpline on 13 11 20 or the NSW Genetics Education Program on (02) 9926 7324 for details of local genetics clinics.

Acknowledgment

This resource is based on an information sheet written by Dr Judy Kirk of the Familial Cancer Service at Westmead Hospital, Sydney. It was jointly produced by the NSW Cancer Council's Cancer Services Unit and the NSW Genetics Education Program.

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