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# There's cancer in the family

**Background**

Patients will sometimes raise the issue of cancer 'running in their family' or it may be identified by the general practitioner when enquiring about a patient's family history.

**Objective**

This article discusses how to deal with concerns about familial cancers including details of the common familial cancer syndromes. It provides further sources of information to use when determining a patient's risk of cancer based on their family history.

**Discussion**

The family history is an important predictor of cancer risk and can be used to tailor cancer prevention strategies and to identify high risk families who may be eligible for predictive genetic testing.

■ **Patients will sometimes raise the issue of cancer 'running in their family' or it may be identified by the general practitioner when enquiring about a patient's family history. Familial clustering of certain cancers was formally described in the 19<sup>th</sup> century by the French surgeon Paul Broca in his 'Traité des tumeurs' recognising the significance of his wife's family of four generations with breast and gastrointestinal cancers. Genetic factors probably play a role in all types of cancer, but certain cancers, such as breast, colorectal and ovarian are more likely to demonstrate familial clustering. However, within these cancers, only 5–10% involve a strongly inherited predisposition.<sup>1</sup>**

**Role of the GP**

The family history needs to be applied systematically in general practice based disease prevention, including using it to assess cancer risk.<sup>2</sup> Identifying people who have a significant family history of cancer can inform surveillance, treatment and, in some families, the offer of predictive genetic testing. *Table 1* describes the key roles for the GP in the context of familial cancers and specific information required when taking a family history.<sup>3</sup> As a general rule, a significant family history is characterised by one or more of the following features:

- multiple close relatives on the same side of the family with cancers of the same or related type
- cancers occurring at an early age
- an individual with two or more primary cancers of the same or different type.

Specific risk assessment and management guidelines exist for familial colorectal, breast, ovarian and prostate cancers, and melanoma. These can be accessed at the 'Genetics in Family Medicine' website (see *Resource*).<sup>3–7</sup> People identified as potentially



high risk should be offered referral to a familial cancer service (FCS) or local genetic counselling service, and those at average and moderate risk, offered disease screening at the respective recommended age and frequency.

### Familial cancer services

These services exist in most Australian states and territories and provide risk assessment, genetic counselling and, if appropriate, genetic testing for a causative mutation (see *Resource*). The service usually confirms cancer diagnoses in relatives to account for the uncertainty in people's self reported family history. Predictive genetic testing to determine risk in unaffected members of high risk families requires the identification of the family specific genetic mutation in an affected relative. Mutation searching for familial cancer mutations is an expensive and often lengthy process that can potentially produce 'uninformative' results.<sup>8</sup> Those found to have inherited a gene mutation that confers a high risk of developing cancer can be offered individualised cancer screening and strategies for prevention. Relatives proven not to have inherited the family specific mutation still have an average risk of developing the cancer based on their age and should follow recommendations for general population screening. However, they can be spared the intensive screening needed by someone who has/may have the mutation.

### Familial colorectal cancer

Between 2–5% of patients with colorectal cancer (CRC) have inherited a known genetic mutation. The types of CRC known to involve genetic susceptibility are familial adenomatous polyposis (FAP) including MUTYL associated polyposis (MAP), and hereditary nonpolyposis colorectal cancer (HNPCC/Lynch syndrome). *Table 2* summarises the genes known to involve genetic susceptibility to CRC. Familial adenomatous polyposis is a rare condition, usually due to a mutation in the adenomatous polyposis coli (APC) tumour suppressor gene. Without treatment, those with proven FAP have a lifetime risk of CRC of almost 100%. Individuals with a mutated APC gene usually develop hundreds of adenomas throughout the colon and rectum that may appear as early as the teenage years. If left untreated, one or more of these adenomas will progress to cancer, often at an early age. Pathological lesions may occur outside the large colon, such as upper gastrointestinal cancer (especially of the duodenum), desmoid tumours and osteomas.

Inheritance of a mutated APC gene follows an autosomal dominant pattern, although in 20–30% of cases there is no family history due to spontaneous mutation. MUTYL associated polyposis is another rare condition similar to FAP except it follows a pattern of autosomal recessive inheritance and is due to mutations in the base excision repair MUTYH gene.

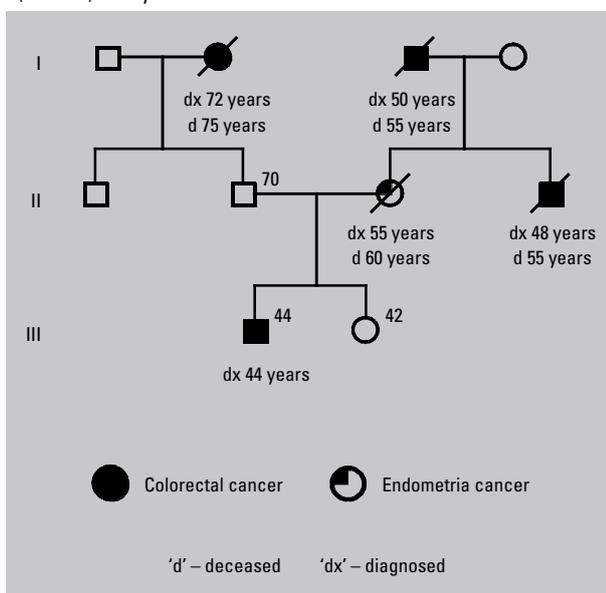
### Management

Management is flexible sigmoidoscopy every 1–2 years starting from age 12–15 years until polyposis develops, then prophylactic

**Table 1. The GP's role in familial cancer**

- Take and keep updated a family history, including:
  - three generations, maternal and paternal first and second degree relatives (where possible)
  - cultural and ethnic background (eg. gene mutations associated with breast and ovarian cancer are more common in Ashkenazi Jews)
  - the primary site and age at diagnosis of any cancer (where possible)
  - using the family history, assess risk according to national guidelines: average or slightly above average, moderate and potentially high risk
- If you are unsure about the significance of the family history, contact a familial cancer service for advice
- Manage average/moderately increased risk patients using the management guidelines
- Refer patients identified at potentially high risk to a familial cancer service or genetics service

**Figure 1. Example of a potentially high risk Lynch syndrome (HNPCC) family**



colectomy. The option of genetic testing and the appropriate age to offer such testing would be discussed at a FCS. Although there is some evidence for COX-2 inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) in polyp prevention, these drugs are not yet used in routine clinical practice.

### Lynch syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, has a lifetime risk of CRC of up to 80% in some families. Inheritance of Lynch syndrome follows an autosomal dominant pattern with incomplete penetrance, meaning that not all individuals with a mutated MMR gene will develop cancer,

Table 2. Genes in which mutations are known to be associated with an inherited predisposition to colorectal cancer and other sites

Inherited cancer syndrome	Mutated gene	Mode of inheritance	Population frequency of mutated gene	Risk of CRC to age 75 years in those identified with a family specific mutation	Other sites with an increased risk of cancer (% lifetime risk)
HNPPC	Mismatch repair (MMR)	Autosomal dominant	~1 in 1000	70–90%	<ul style="list-style-type: none"> <li>• Endometrium (40%)</li> <li>• Ovary and stomach (10%)</li> <li>• Urinary tract, small intestine, pancreas and biliary tree</li> </ul>
FAP	APC	Autosomal dominant	~1 in 10 000	90–100%	<ul style="list-style-type: none"> <li>• Duodenum (5%)</li> </ul>
MAP	MUTYH	Autosomal recessive	~1 in 50–100	Under investigation, thought to be 90–100%	<ul style="list-style-type: none"> <li>• Duodenum (4–25%)</li> </ul>

and so in some cases, there is no family history. Nevertheless, individuals most likely to have a mutated MMR gene have a strong family history of CRC, characterised by early age of onset (<50 years) and a tendency for proximal colonic malignancy or multiple CRCs (Figure 1).

Cancers occurring outside the large colon may also be a feature, most commonly endometrial cancer, but also cancers of the ovary, stomach, small bowel, renal pelvis, ureter, biliary tract, and, more rarely, the brain. Cancers associated with Lynch syndrome tend to show high levels of microsatellite instability and may lack immunohistochemical expression of MMR proteins in tumour tissue. Consideration of tumour testing should be given for all patients diagnosed with CRC aged 50 years or less, or where there is a suggestive family history.

### Management

Patients with Lynch syndrome should be offered a colonoscopy every 1–2 years from age 25 years, or 5 years earlier than the youngest diagnosis in the family (whichever comes first). Faecal occult blood testing (FOBT) may be offered in alternate years or to patients unwilling to accept colonoscopy. Options for surveillance at other sites, risk reducing surgery, and genetic testing would be discussed by a FCS.

### Familial breast/ovarian cancer

At least 1–5% of breast cancers, and 5–10% of ovarian cancers involve the inheritance of a known genetic mutation. Mutations in the BRCA1 and BRCA2 genes are associated with both breast and ovarian cancer. Mutations in other genes are also associated with an increased risk of developing breast or ovarian cancer, as well as some other cancers (Table 3). However, the majority of affected women do not carry an inherited mutation in a known breast or ovarian cancer predisposing gene. Individuals most likely to have a mutated BRCA 1 or BRCA2 gene have a strong family history of cancer that may include:

- breast cancer before the age of 40 years
- bilateral or male breast cancer

- combination of breast and ovarian cancers
- Ashkenazi Jewish ancestry.

Inherited mutations in BRCA1 and BRCA2 genes follow an autosomal dominant pattern of inheritance and can be inherited from either parent (Figure 2).

### Management

Women at potentially high risk of breast and ovarian cancer, based on current risk assessment criteria, should be offered referral to a FCS for detailed risk assessment and management planning. Genetic testing may be available if the woman wishes to clarify her genetic risk or that of her family, or wishes to consider risk reducing surgery. A FCS will develop an individual surveillance program that may include: regular clinical breast examinations; annual mammography, potentially with additional imaging techniques such as magnetic resonance imaging (MRI); surveillance for ovarian cancer with CA-125 and transvaginal

Figure 2. Example of a potentially high risk breast/ovarian cancer family

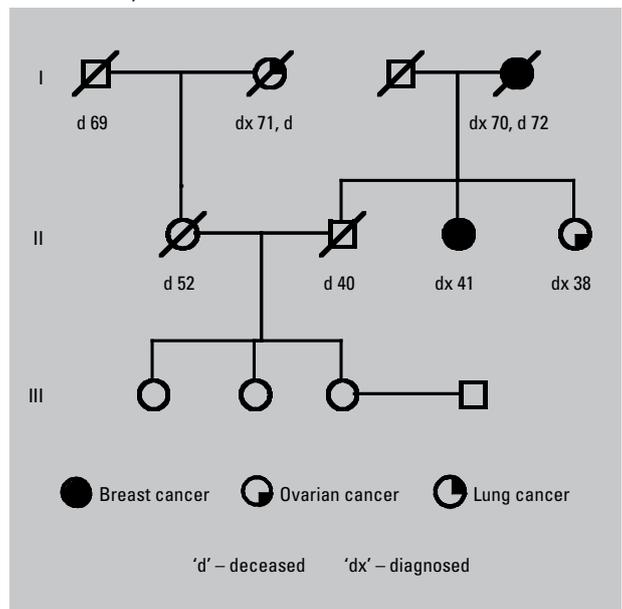




Table 3. Genes in which mutations are known to be associated with an inherited predisposition to breast or ovarian cancer and possible cancer at other sites

Gene	Mutation frequency	Major sites at risk	Risk of cancer at age 75 years where a family specific mutation has been identified*	Other sites with up to a 10% lifetime risk
BRCA1	1/1000**	Breast Ovary	40–80% 10–60%	Prostate
BRCA2	1/1000**	Breast Ovary	40–80% 10–40%	Male breast, prostate, pancreas
P53 (Li Fraumeni syndrome)	1/10 000	Breast Bone, soft tissue	50% <10–50%	Brain, lung, adrenal gland
Mismatch repair genes (HNPCC)	1/1000	Large colon Uterus	50–80% 50%	Ovary, other gastrointestinal, renal tract

\* There is a wide range of risk associated with mutations in these genes \*\* 1/100 for individuals of Ashkenazi Jewish ancestry

ultrasound; risk reducing mastectomy or salpingo-oophorectomy; and participation in a clinical breast cancer prevention trial (eg. IBIS II).

## Melanoma

An inherited mutation in certain genes is thought to be involved in up to 5% of cases of melanoma. Two genes have so far been identified which are associated with a predisposition to melanoma: CDKN2A and CDK4. CDKN2A mutations have been found in 20–50% of families in different populations with three or more affected first degree relatives. Mutations in the CDKN2A and CDK4 genes follow an autosomal dominant pattern of inheritance and are associated with the following personal or family history characteristics:

- three or more first or second relatives with melanoma
- several primary melanomas in one relative
- diagnosis of first melanoma aged less than 40 years
- the presence of multiple atypical naevi early in life.

These families would be candidates for participating in research programs where genetic testing for mutations in candidate genes may be performed.

## Management

All individuals at potentially high risk of melanoma should be offered referral to a FCS. Surveillance should be arranged in association with a FCS, and discussions will include: education about sun protection and early detection; intensive surveillance, commencing from age 10 years, including 3 monthly self examination, whole body photography and skin surface microscopy; skin and scalp examination by a dermatologist at least annually; and a low threshold for the excision biopsy of any suspicious lesions.<sup>7,9</sup>

## Prostate cancer

Men with a first degree relative with prostate cancer diagnosed before 60 years of age have at least a twofold increased risk of prostate cancer. This risk is further increased in families where

two or more members on the same side of the family are affected. Male carriers of a mutation in either BRCA1 or BRCA2 have up to a 10% lifetime risk of prostate cancer. Current recommendations are to offer digital rectal examination (DRE) and prostate specific antigen (PSA) screening to men aged over 50 years who have a first degree relative with prostate cancer diagnosed before 60 years of age. Other genes associated with risk of prostate cancer are still under investigation. A recent Swedish study identified five common single nucleotide polymorphisms (SNPs), which, in combination with family history, are strongly predictive of prostate cancer.<sup>10</sup> In the future, genetic testing may eventually be used to accurately identify high risk men who may benefit most from targeted prostate cancer screening.

## Rare cancer syndromes and other familial clustering

There are several other rare cancer syndromes for which genetic testing is available in Australia. These include Von Hippel-Lindau syndrome (VHL syndrome), Li Fraumeni syndrome and multiple endocrine neoplasia (MEN) 1 and 2.

Von Hippel-Lindau syndrome affects approximately 1 in 36 000 births and is characterised by haemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma; and endolymphatic sac tumours. It is caused by a mutation in the VHL tumour suppressor gene which follows an autosomal dominant pattern. Twenty percent of cases of VHL are a result of a sporadic gene mutation.

Li Fraumeni syndrome is due to mutations in the p53 gene and affects approximately 1 in 10 000 births. It is associated with early onset breast cancer, childhood sarcomas, brain and adrenocortical tumours and leukaemias.

Both MEN 1 and MEN 2 have a population frequency of approximately 1 in 30 000 births. Multiple endocrine neoplasia 1 is characterised by the development of a combination of endocrine tumours including: parathyroid, pituitary and carcinoid tumours, and



endocrine tumours of the gastro-entero-pancreatic tract. In contrast, MEN 2 is characterised by the development of medullary carcinoma of the thyroid and pheochromocytoma. Both MEN 1 and 2 follow an autosomal dominant pattern of inheritance, however 10% of MEN 1 cases and 5% of MEN 2 cases are sporadic.

Sometimes patients will present with other apparent clusters of unusual cancers in their family. Occasionally these will be due to a specific rare inherited cancer syndrome, but often this represents chance clustering which has no clinical relevance to the patient's risk of cancer. If in doubt, a FCS will usually be able to provide advice, either by telephone or letter, as to the likelihood of an inherited cancer syndrome.

## Summary

If a patient is concerned that 'there is cancer in the family', obtain a detailed family history, which often involves sending the patient to find out more information from their relatives. This can be facilitated by use of a family history questionnaire (see *Resource*).<sup>11</sup> Use existing risk assessment guidelines for the common familial cancers, and if in doubt, contact your FCS. You will often be able to reassure your patient that cancer does not truly run in their family.

## Resource

Genetics in Family Medicine – risk assessment and management guidelines, details of familial cancer services in Australia, and family history questionnaire. Available at <http://gpgenetics.edu.au/index.html>.

Conflict of interest: none declared.

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