Familial aspects of cancer

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While cancer may affect up to one third of the Australian population in their lifetime, up to 10% of common cancers are familial, particularly breast/ovarian and bowel, with a significant genetic susceptibility component. Not all susceptible individuals and family members develop a particular cancer and their clinical spectrum overlaps with families where cancer is more likely due to other factors (e.g. environmental).

A range of genes, if mutated, can now be identified as causing a high risk of cancer. Currently, the process of selecting this group for more detailed management relies on family history or particular pathological analysis of individual cancers – histopathology, immunohistochemistry (IHC), and microsatellite instability (MSI; in the case of Lynch Syndrome).

The family doctor is well placed to judge the relevance of family history and presentation of cancer [1] with respect to hereditary risk, by using differing selective criteria (see Table 1). However, in a general sense, an autosomal dominant inheritance is suggested by this pattern over two or more generations:

- Multiple (≥3) first degree relatives (on same side of family) have the same or related cancers.
- Occurrence at an earlier age (<50 years)
- One individual with ≥2 primary cancers of one or more types [2].

Such features should prompt referral to a Familial Cancer Clinic, such as the Genetic Services of WA, a multidisciplinary clinic consisting of cancer genetic counsellors, clinical geneticists, molecular scientists and relevant consultants.

Cancer genetic counsellors construct a detailed family history, often with the advantage of access to family data (confidential or unknown to the patient), or by consented access to medical and surgical details (e.g. histopathology reports).

The patient is then given an inherited risk analysis for their cancer, the likelihood of recurrence, whether other systems may be affected and potential risks for other family members. A plan for ongoing cancer screening (surveillance) and further preventive measures are discussed and documented for patient and referring doctor.

Aspects of gene mutation analysis are fully discussed with the patient, including the probable time for a report to be issued and the likelihood of an inconclusive outcome. The latter may occur where an apparent mutation is identified but its pathogenicity cannot be confirmed by reference to functional analysis, phylogenetic preservation and other international databases etc.

A positive diagnostic mutation analysis that confirms the high hereditary nature of a cancer aids screening compliance amongst notified family members also at risk. The usual autosomal dominant inheritance means that many will not carry the specific family cancer predisposing mutation.

SOURCE: Medical Forum WA magazine, December 2010 edition

Table 2: Some Known Cancer Predisposition Genes (dominant inheritance)

Hereditary syndrome	Commonest cancers	Gene
Familial adenomatous polyposis	Colon, duodenum, periampullary	APC
Lynch Syndrome . Muir-Torre S. Turcot S.	Colon, endometrium, ovary, stomach, small bowel, renal tract, pancreas, biliary tract	hMSH2 hMLH1 hMSH6 hPMS2
Peutz-Jeghers syndrome	Gastrointestinal tract, pancreas, ovary, testis, breast, uterus	STK11
Breast cancer, breast/ ovarian cancer	Breast, ovary, prostate	BRCA1 BRCA2
Melanoma	Melanoma, pancreas	CDKN2A/ p16INK4A CDK4
Li-Fraumeni	Sarcoma, breast, brain, leukaemia, adrenocortical	p53
Neurofibromatosis I	Neurofibrosarcoma, phaeochromocytoma, optic glioma	NF-1
Neurofibromatosis 2	Vestibular Schwannomas Schwannomas of other cranial or peripheral nerves Meningiomas	NF2
Von Hippel-Lindau syndrome	Haemangioblastoma of retina and central nervous system, renal cell carcinoma, phaeochromocytoma	VHL
Multiple endocrine neoplasia type 1 Multiple endocrine neoplasia type 2A and 2B Medullary thyroid carcinoma	Parathyroid,pancreatic islet, pituitary adenoma, adrenal Medullary carcinoma of the thyroid, phaeochromocytoma	MEN1 RET RET
Retinoblastoma	Retinoblastoma, osteosarcoma	RB1
Phaechromocytoma		RET VHL SDHD SDHB
Tuberous sclerosis	Angiomyolipoma	TSC2
Cowden syndrome	Breast, thyroid, other	PTEN
Birt-Hogg-Dubé	Renal oncocytoma and renal cell carcinoma Cutaneous Fibrofolliculomas	FLCN

Adapted from App C: Known Cancer Predisposition Genes. Clinical Practice Guidelines. Familial aspects of cancer: A guide to clinical practice. NHMRC.

Table 1: Breast/ovarian cancer

Breast cancer

Moderately increased risk

- One 1° relative with breast cancer before the age of 50*
- Two 1° relatives, same side of the family, with breast cancer*
- Two 2° relatives, same side of the family, with breast cancer, at least one before the age of 50.*

Potentially high risk

1. Two 1° or 2° relatives, on one side of the family, diagnosed with breast or ovarian cancer plus one or more of the following features on the same side of the family:

- Additional relative(s) with breast or ovarian cancer
- Breast cancer diagnosed before the age of 40
- Bilateral breast cancer
- Breast and ovarian cancer in the same woman
- Ashkenazi Jewish ancestry
- Breast cancer in a male relative

One 1° or 2° relative diagnosed with breast cancer at age 45 or younger plus another 1° or 2° relative, same side of the family, with sarcoma (bone/soft tissue) at age 45 or younger

** Without the additional features of the high risk breast/ovarian cancer group*

Adapted from National Breast Ovarian Cancer Centre. Advice about familial aspects of breast cancer and epithelial ovarian cancer: a guide for health professionals, 2006.

Predictive testing in a well person who has not had cancer is often stressful and conducted only after preliminary counselling with full understanding of the potential medical and psycho-social implications of results. Implications to life assurance, disability or income protection are also discussed.

For those family members who receive negative mutation results there is reassurance that they and their descendants are not at high risk of the family cancer. This desirable result can be accompanied by responses such as survivor guilt, denial, or false invincibility and reassurance.

A positive mutation result prompts appropriate surveillance and management, which may include prophylactic surgery. Such programs reduce morbidity and mortality and are cost effective. For some familial cancers, such as adenomatous polyposis (FAP), where the risk of bowel cancer and surgery approaches certainty, family planning may include prenatal diagnosis or pre-implantation genetic diagnosis (PGD) to avoid a descendant carrying the family cancer mutation.

Testing and surveillance require patient resolve, and may be accompanied by alienation or disruption of family relationships, anxiety and or depression. Therefore, the long term role of the family practitioner to support patients in these circumstances is most important.

Table 2 gives an indication of some of the cancer predisposition gene mutations that may be identified by PathWest Molecular DNA Laboratories. ■

References:

1. Weller, DP, Harris MF, Cancer Cure: What role for the general practitioner, MJA 2008; 189 (2): 59-60.

2. Emery J, Barlow-Stewart K, Metcalfe SA, There's cancer in the family, Australian Family Physician 2009; 38 (4): 194-198.

National Health and Medical Research Council. Clinical Practice guidelines. Familial Aspects of Cancer: A guide to Clinical Practice. www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/Cp67.pdf