THE ROLE OF FAMILIAL CANCER SERVICES

Judy Kirk ■ Familial Cancer Service, Westmead Hospital, Westmead, NSW ■ Email: judy_kirk@wmi.usyd.edu.au

Abstract

There is now an improved ability to detect people at high-risk of cancer through analysis of their family history and genetic testing. Advances in cancer screening, cancer surveillance and cancer prevention have accompanied this. It is important to identify individuals at high cancer risk so that these advances can be applied in their management. Equally important, is the identification of those not at high-risk, so that they are spared unnecessary cancer screening and concern. Risk assessment and genetic testing is available in Australia through familial cancer services. This article introduces the common syndromes requiring referral to such a service and the general principles of cancer genetic testing.

Cancer is a genetic disease

Cancer is a genetic disease, associated with alterations (mutations) in genes that normally act to control cell growth, proliferation and DNA repair. These genetic mutations (genetic "hits") usually occur in somatic (tissue) cells over the course of a lifetime. In this way, cancer is usually due to a series of acquired mutations in genes that control cell growth, eventually allowing cells with these faults to grow in an uncontrolled fashion. Up to 95% of all cancers are caused by these somatic mutations in cancer-associated genes. Because they occur in somatic cells, they are not inherited.

However, some rare families have an inherited mutation in one of these same genes. In these families, the "first hit" is inherited either in the egg or the sperm (this is known as a germline mutation). It affects all cells of the body. People who inherit a germline mutation in a cancer-associated gene are at increased risk of developing cancer. The pattern of cancer seen in such a family will depend on the specific gene involved and sometimes on the type and location of mutation in that gene.

There have been considerable advances in the area of cancer genetics over the last 15 years, with the identification and characterisation of genes in which germline mutations predispose to a high risk of cancer. These scientific advances in understanding the genetic predisposition have been translated into clinical practice as genetic testing for families with cancer predisposition has become available. This has been achieved by the development of familial cancer services throughout major centres in Australia, often within public-sector comprehensive cancer centres. Such services are staffed by clinical geneticists and/or oncologists with expertise in cancer genetics, supported by trained genetic counsellors and a molecular genetics laboratory. The role of the familial cancer service is to identify individuals at high genetic risk of cancer so that appropriate intervention strategies can be implemented for early detection or prevention, with the ultimate aim being to reduce the impact of cancer for the individual and their family.

Genetic predisposition to cancer

Family history has long been recognised as an important risk factor for cancer. The taking of a good family history is more important than ever.[1] National guidelines can assist health professionals to estimate the risk of cancer based on family history and to determine whether referral to a familial cancer service might be appropriate.[2,3] In general, family histories of cancer that suggest genetic susceptibility include those with either three or more relatives on the same side of the family with the same (or related) cancer, or two affected individuals with the same (or related) cancer where there is an additional "high risk feature", such as earlier than average age at diagnosis or the presence of more than one primary cancer in a family member.

The role of the familial cancer service

A familial cancer service can be expected to construct a full three-generation pedigree on both sides of the family. Importantly, family history is often poorly reported and verification of the described family history is necessary. Gynaecological malignancy is commonly misreported and confirmation that the family account of ovarian cancer was actually a cervical intra-epithelial neoplasia, or that a reported breast cancer was simply a fibroadenoma, can dramatically change the assessment of familial risk. Verification of family history involves the genetic counsellor obtaining consent from family members to enable access to pathology reports and medical records.

At the clinic visit, an assessment of cancer risk may be made on the basis of family history, but this is generally a broad categorisation, placing an individual at "average risk", "moderate risk" or "potentially high risk", based on national guidelines. For those at potentially high-risk, due to a stronger family history, genetic testing (discussed below in further detail), can assist in further clarifying risk within some families. An offer of genetic testing can only be made if there are known genes in which heritable mutations cause an increased risk of cancer.

The well-known cancer susceptibility syndromes are reviewed in Nagy and Garber for general reference and further information is available through Australian websites.[4–7] It should be recognised that genetic testing is now a mandatory part of the clinical management of Multiple Endocrine Neoplasia (Types 1 and 2), retinoblastoma, Familial Adenomatous Polyposis (FAP)

and Von-Hippel Lindau syndrome, where the genes tested are MEN1, RET, Rb, APC and VHL, respectively. In these conditions there is a clear role for screening and prevention in reducing the impact of cancer for those at proven high-risk.[6,7]

For families with a strong family history of breast and ovarian cancer, clinical testing usually involves the genes BRCA1 and BRCA2. Breast and thyroid malignancies with intestinal hamartomas (consistent with Cowden syndrome) may be investigated by testing the PTEN gene. A family history of bowel cancer, especially early onset (aged <50 years) and other cancers, including uterus, ovary, stomach, small bowel, renal pelvis or ureter, suggests the involvement of the mismatch repair genes in the syndrome of Hereditary Non-Polyposis Colon Cancer (HNPCC). Genetic testing for other polyposis syndromes, including Juvenile Polyposis and Peutz-Jeghers syndrome is now possible. On the other hand, genetic testing for familial melanoma is usually only available when a family CDKN2A mutation has already been identified as a result of participation in a research study. Furthermore, despite intensive research, no genes have yet been firmly identified in which mutations cause a hereditary tendency to prostate cancer. Finally, for some syndromes, such as the Li-Fraumeni syndrome, where there is a high risk of varied cancers (including paediatric sarcoma, haematological malignancy, early onset breast cancer, adrenal cancer, brain tumour and lung cancer), genetic testing for p53 may identify a causative mutation. However, for individuals with the Li-Fraumeni syndrome, there is currently little to offer in the way of proven screening or prevention, and so genetic testing needs to be considered with care.

Families with a significant family history of cancer can be enrolled in studies involved in genetic research. Australian research efforts, such as the Kathleen Cuningham Consortium for Research on Familial Breast Cancer (kConFab), the Australian Breast Cancer Family Study (ABCFS) and Australasian Colorectal Cancer Family Study (ACCFS) will continue to make significant contributions to understanding the familial aspects of cancer.

Genetic testing for cancer susceptibility

In April 2003, the American Society of Clinical Oncology (ASCO) published an updated policy statement concerning genetic testing for cancer susceptibility: "ASCO recommends that genetic testing be offered when:

1) The individual has personal or family history features suggestive of a genetic cancer susceptibility condition;
2) The test can be adequately interpreted; and
3) The results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer. ASCO recommends that genetic testing only be done in the setting of pre and post-test counselling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities." [8]

It is recommended that prior to consideration of cancer genetic testing, key components of the consultation should include medical and family history, cancer risk assessment and discussion of the limitations, as well as possible risks (eg. impact on future applications for life/disability insurance) and benefits of molecular genetic testing for the person and their family members. Informed consent must be obtained.[9]

Genetic testing is now available through familial cancer services for some of the common hereditary cancer syndromes listed above. Whatever the gene to be tested, the general principles remain the same. The first step in genetic testing is usually to take blood from one of the family members affected by the condition, although sometimes an unaffected obligate carrier may be tested instead. This must be done with fully-informed consent. Counselling before testing must cover the potential harms, benefits and limitations of such testing. The laboratory then searches the relevant gene(s) to determine whether a causative gene mutation can be found.

This first phase, the "mutation search", may take some months. A causative gene mutation cannot be found in every family, as mutations may be missed, or mutations may be present in other genes that are not yet identified. Importantly, this means that if the family history is strong and the genetic test (mutation search) fails to identify a gene mutation in an affected family member, that test result should be considered "inconclusive" and all relatives remain at potentially high-risk. However, if a causative mutation is identified in the relevant gene (eg. in BRCA1 or BRCA2 for a breast cancer family, or in a mismatch repair gene for an HNPCC family), then other at-risk family members (males and females) can be offered "predictive" genetic testing. Predictive tests are relatively cheap and quick, with results generally available in four to six weeks. Once the family gene mutation has been identified in the mutation search phase, others in the family can simply be tested for the presence or absence of that same gene fault.

The risk of cancer associated with the gene mutation and the approach to that risk requires discussion before testing. Those who are found not to carry the family mutation (at predictive testing), should be considered to be at average risk of cancer. They and their offspring can be spared unnecessary cancer screening and concern.

Predictive genetic testing for cancer risk is usually restricted to adults unless there is a case for medical intervention in childhood, such as in families with Familial Adenomatous Polyposis, where screening starts in the teenage years. Pre-natal testing and pre-implantation genetic diagnosis is feasible once the family mutation is identified, but is not often considered in cancer families.

Conclusion

Genetic susceptibility to cancer is rare. It can generally be identified by taking a good family history. If genetic testing identifies a causative gene mutation, then predictive testing can identify those family members who do not carry the mutation and are "not at risk". It

also identifies those who are "at high risk". The latter can take the opportunity to have intensive cancer screening including newer modalities, such as breast magnetic resonance imaging. They may wish to consider risk-reducing surgery, particularly in circumstances where this has a proven role.

Restorative procto-colectomy is the standard care for preventing bowel cancer in FAP, as the risk of cancer without such intervention is 100%. In carriers of a BRCA1 or BRCA2 gene mutation, risk-reducing salpingo-oophorectomy not only dramatically reduces the risk of ovarian cancer, but if done before menopause, halves the risk of breast cancer. Prophylactic mastectomy (with or without reconstruction) also significantly reduces the risk of breast cancer. For children with an inherited RET gene mutation, prophylactic thyroidectomy prevents medullary thyroid cancer. In some cases chemoprevention can be used to reduce the risk of cancer. Tamoxifen may be considered as a risk-reducing option for high-risk women, although there are side-effects and evidence is not yet available regarding the impact of preventative tamoxifen on mortality from breast cancer.

Finally, for those at high genetic risk who do develop cancer, targeted therapies are being designed for tumours, depending on their molecular basis. As an example, BRCA1/2 deficient breast/ovarian cancers seem to rely on poly (ADP-ribose) polymerase (PARP) in response to DNA damage and specific inhibition. Using PARP inhibitors is now being studied in a Phase II trial of recurrent breast/ovarian cancers in BRCA1/2 carriers. Such developments will no doubt continue.

The improved ability to detect people at high-risk through analysis of their family history and genetic testing has been accompanied by advances in cancer screening, cancer surveillance and cancer prevention. It is important to identify these individuals so that these advances can be applied in their management, offering hope of making an impact on the national goals of cancer control.

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