



# Cancer Genetics Gazette



A newsletter for specialist clinicians from the Familial Cancer Unit  
November 2007 | Issue 4

Welcome to the 2nd edition of the Cancer Genetics Gazette for 2007. We have two feature articles in this edition including **'The management of BRCA-associated breast cancer'** (by Dr James Kollias) and **'Familial colorectal polyposis syndromes'** (by Dr Daniel Worthley and Dr Lara Lipton). We hope you enjoy this bumper issue!

## In focus

### The management of BRCA-associated breast cancer

#### Case study

A 39 year old woman attended for her annual breast cancer surveillance appointment. There was a strong family history of breast cancer – mother and maternal grandmother diagnosed with breast cancer at age 46 years and 54 years respectively. There was no palpable abnormality in either breast or axillary area. Mammography did not demonstrate any abnormality. However, ultrasound demonstrated a 1.4 cm malignant mass and cytology confirmed malignant cells. After staging investigations excluded metastatic disease, the patient underwent partial mastectomy and sentinel node biopsy. Histopathology revealed a 16mm high-grade breast cancer with clear resection margins. The two sentinel nodes were free of metastatic tumour. The tumour did not stain for oestrogen or progesterone receptor and was HER2 negative according to FISH. The patient was recommended adjuvant chemotherapy and breast irradiation. During chemotherapy, she was assessed by the Familial Cancer Unit and was found to harbour a pathogenic germline mutation in the BRCA1 gene. The patient was subsequently offered the option of bilateral mastectomy with immediate breast reconstruction upon completion of chemotherapy, obviating the need for breast radiotherapy. Due to the increased risk of ovarian cancer, bilateral salpingo-oophorectomy was also offered. She opted to continue with the previous plan of adjuvant chemotherapy, breast irradiation and regular follow-up. She may consider bilateral mastectomy and/or oophorectomy at a later date.

#### Introduction

The case study illustrates the clinical dilemmas faced by BRCA1/2 patients who are diagnosed with breast cancer. Like other patients with a newly diagnosed breast cancer, women with a strong family history of breast/ovarian cancer or those with a known BRCA1/2 mutation must contend with the psychological stress of the breast cancer diagnosis, survival issues, and the effects of breast cancer treatments. However, such women also contend with issues of a possible increased risk of ipsilateral breast cancer recurrence, contralateral breast cancer and ovarian cancer. There is a natural tendency to recommend radical surgical interventions such as bilateral mastectomy and oophorectomy for such patients. Although this may be justified in some cases, it is questionable in others. The following article explores the various issues of competing risks for women diagnosed with early breast cancer who have a BRCA mutation or have a strong family history of breast/ovarian cancer.

#### Breast conserving therapy for BRCA mutation carriers or those with a strong family history

##### *Radiotherapy sensitivity*

The BRCA1/2 genes are involved in the cellular response to DNA damage, but their molecular functions are not fully understood. Preclinical evidence of radiation sensitivity has led to concerns regarding radiation-induced complications in patients with BRCA1/2 mutations. Despite this, no studies have demonstrated evidence of increased radiation sensitivity or sequelae in breast tissue heterozygous for BRCA1/2 germline mutation compared with controls.<sup>1</sup>

##### *Local recurrence issues*

Breast-conserving therapy (partial mastectomy and radiotherapy) is recommended for the majority of women with early-stage breast cancer, but its appropriateness in patients with germline mutations in BRCA1 or BRCA2 remains controversial.

Women with sporadic breast cancer have a low risk of local recurrence, with an annual incidence of 0.5 – 1.5%. For women with hereditary breast cancer, several studies have failed to demonstrate any difference in recurrence rates and overall survival comparable to those in sporadic disease controls in the short term.<sup>2,3</sup> However, with longer

follow-up, there is an increase in late second primary breast cancers, where the annual incidence may be higher – approximately 2 – 3%.<sup>3,4</sup> In most cases, late recurrence is situated away from the primary tumour site, indicating the likelihood of new primary tumours within the breast.<sup>5</sup>

Other studies have also suggested that age of onset is a more significant factor affecting recurrence, where women with BRCA-associated breast carcinoma who undergo breast conserving therapy appear to have risks of local recurrence similar to those reported for young women without known mutations. It has been suggested that the indications for breast conserving therapy in this group of women should be the same as those for women with nonhereditary carcinoma.<sup>6</sup> The use of Tamoxifen and/or chemotherapy has not been demonstrated to significantly reduce local recurrence after breast conserving treatment in BRCA1/2 mutation carriers<sup>6</sup>.

#### *Survival after breast conserving therapy*

Overall, no studies have demonstrated that breast conserving treatment leads to any survival disadvantage for women with hereditary breast cancer compared with sporadic disease.

#### **Contralateral breast cancer**

Contralateral breast cancer risk in BRCA1/2 patients is higher than for sporadic cases of breast cancer. For cases of newly diagnosed hereditary breast cancer the annual contralateral breast cancer risk varies between 2-4% compared with cases of sporadic breast cancer, where the annual incidence is 0.4 – 0.6%.<sup>4,7</sup> Early age of onset in BRCA mutation carriers or those with hereditary non-BRCA1/2 are associated with an increased contralateral breast cancer risk. Despite this observation, overall survival is not compromised, probably due to the early detection of the contralateral breast cancer.<sup>8</sup>

#### **Breast cancer surveillance**

Annual mammography is recommended for surveillance of the ipsilateral breast after breast conserving treatment and of the contralateral breast in women with sporadic breast cancer. Breast surveillance strategies for BRCA1/2 mutation carriers after breast cancer treatment are not well defined. MRI has recently been shown to be an effective breast cancer screening modality in asymptomatic young women with BRCA1/2 mutations,<sup>9</sup> but its role in follow-up surveillance has yet to be determined. Currently, annual mammography +/- ultrasound is used for breast cancer surveillance.

#### **Ovarian cancer**

Bilateral salpingo-oophorectomy after diagnosis of early breast cancer in women with hereditary breast cancer could be considered for two reasons. In premenopausal

women with moderate/high-risk oestrogen receptor (ER) positive breast cancer, oophorectomy reduces the risk of systemic relapse by 30-40%.<sup>10</sup> This is pertinent for BRCA2 breast cancer which is more likely to be sensitive to oestrogen. Secondly, BRCA mutation carriers are at high risk of carcinomas of the ovaries and salpinges. Bilateral salpingo-oophorectomy reduces the risk of cancer by 90-95%.<sup>11</sup> The 10 year cumulative risk of ovarian cancer in BRCA mutation carriers diagnosed with early breast cancer is 13% for BRCA1 and 7% for BRCA2.<sup>12</sup> The use of chemotherapy or tamoxifen does not appear to have an impact on ovarian cancer risk in such women. More importantly, ovarian cancer accounts for 25% of deaths in BRCA women previously treated for breast cancer. The high incidence of ovarian cancer and its impact on survival and/or breast cancer local recurrence suggests that oophorectomy should be offered to female BRCA1 and BRCA2 mutation carriers with a diagnosis of breast cancer, especially those with stage I disease.

#### **Survival**

Despite the apparent increase in local recurrence after breast conserving treatment, contralateral breast cancer and ovarian cancer in patients with BRCA1/2 mutations, their survival prospects are similar to women with sporadic breast cancer.<sup>3, 13, 14</sup> Women with BRCA1 mutations appear to have a worse prognosis than those with BRCA2 mutations.

#### **Summary**

The treatment options for women with hereditary forms of breast cancer are complicated by the perceived increased risks of local recurrence after breast conserving therapy, contralateral breast cancer and ovarian cancer. Despite this clinical dilemma, there is no current evidence to suggest that radical treatments (ie bilateral mastectomy) confer a survival benefit in such cases. The prognostic features of the primary breast cancer must be interpreted and highlighted. For example a patient with a large, high grade breast cancer with extensive lymph node involvement is unlikely to benefit from radical treatments due to her poor survival prospects. On the other hand, a young woman with an extensive area of high-grade ductal carcinoma *in-situ* (DCIS) requiring mastectomy or a small high-grade lymph node negative cancer has excellent survival prospects where the risks of a subsequent potentially life-threatening contralateral breast cancer or ovarian cancer may be of clinical significance. Radical surgical treatments may assume greater importance in these situations.

The complexities of treatment for women with hereditary breast cancer highlight the need to discuss such cases in multidisciplinary forums including surgical oncologists, medical oncologists, radiation oncologists, breast radiologists, pathologists, cancer geneticists, specialist breast nurses and general practitioners. Hereditary breast cancer patients with a newly diagnosed breast cancer

should be offered standard breast cancer management but be made aware of the other issues mentioned above. Some patients may choose radical treatments from the outset. However, in many cases, the issue of 'risk reduction surgery' can be raised at a convenient time after completion of adjuvant treatments for breast cancer when the acute anxiety associated with the breast cancer diagnosis and therapy has settled.

**Author:**

**Dr James Kollias** – MBBS, FRACS, MD  
Breast & Endocrine Surgeon  
Chairman Breast Section, RACS  
Surgeon, CNAHS & BreastScreen SA

*References available upon request to the Cancer Genetics Education Project Officer on 08 8291 4269 or genetics@cancersa.org.au*

## **Familial colorectal polyposis syndromes: when to suspect, how to test and what to do.**

### **Introduction**

The diagnosis and management of familial colorectal cancer (CRC) syndromes represents a great triumph in the translation of molecular genetics into clinical practice. These successes have brought new challenges and, although genetic testing and colorectal surveillance reduces cancer-specific mortality in affected families<sup>1,2</sup> and should theoretically be able to prevent CRC in these families altogether, many individuals remain unrecognised or unwilling to accept genetic testing and appropriate surveillance. This article provides a brief clinical overview to help recognise, classify and manage inherited colorectal polyposis syndromes.

### **Colorectal cancer syndromes**

Inherited CRC syndromes include those characterized by multiple colorectal adenomas, such as familial adenomatous polyposis (both classical FAP and attenuated FAP or AFAP) and *MUTYH*-associated polyposis (MAP).<sup>3</sup> Other polyposis syndromes are characterized by hamartomas, such as juvenile polyposis syndrome and Peutz-Jeghers syndrome, others by hyperplastic polyps<sup>4</sup> or a mixture of pathologies.<sup>3</sup> In addition Lynch syndrome, or hereditary non-polyposis colorectal cancer, is associated with colorectal as well as other gastrointestinal and extra-alimentary tract malignancies, in the absence of multiple colorectal adenomas. This report will concentrate on the adenomatous polyposis syndromes FAP, AFAP, and MAP. These conditions are rare, comprising <1% of CRC cases, but they are extremely important to recognise because of the great potential benefit not only to the individual patient, but to their family.

### **Familial Adenomatous Polyposis**

Classical FAP is an autosomal dominant syndrome, defined by the presence of adenomatous polyposis (>100 colorectal adenomas). The adenomas are usually evident by late teenage years and in the absence of prophylactic colectomy, CRC occurs in essentially all cases by the age of 50 years.<sup>3,5</sup> FAP results from a pathogenic mutation in the *Adenomatous Polyposis Coli (APC)* gene, an important tumour-suppressor gene with widespread functions. Interestingly, the site of mutation within *APC* influences the resultant clinical phenotype both in terms of associated extra-colonic features such as desmoid tumours and congenital hypertrophy of the retinal pigment epithelium (CHRPE), as well as severity of polyposis.<sup>3</sup> Generally, mutations around codon 1300 of the *APC* gene, the 'mutation cluster region', are associated with a higher colorectal polyp burden, whilst mutations at the 5' or 3' ends of the gene result in a milder phenotype, AFAP. AFAP is characterized by <100 colorectal adenomas, and the mean age of development of CRC is delayed by approximately 15 years compared to classical FAP.<sup>3</sup>

*APC* mutation testing, conducted through regional or state-based clinical genetics services, should be considered for patients that satisfy the criteria for classical FAP (>100 adenomas) or AFAP, and in the first degree relatives (sibling, parents, children) of those with an informative *APC* mutation (Box 1). Genetic testing of relatives (predictive testing) is only valuable when a pathogenic mutation can be confirmed in the proband. *APC* mutations are discovered in about 85% of Australian patients with classical FAP.<sup>5</sup> In families without an informative mutation to allow predictive testing, clinical screening of at risk family members by flexible sigmoidoscopy is recommended. CHRPEs when present, may also help to confirm the diagnosis in unaffected relatives, although interpretation of pigmented retinal lesions requires an experienced, specialist ophthalmology service.<sup>6</sup>

Flexible sigmoidoscopy or colonoscopy is necessary to screen susceptible relatives for FAP and also to help guide referral for prophylactic colectomy in those affected. Screening and surveillance with annual flexible sigmoidoscopy should begin at 12 to 15 years or from the time of diagnosis, respectively.<sup>5</sup> Chromoendoscopy, in which dye is sprayed onto the colorectal mucosa at the time of sigmoidoscopy, enhances detection of small adenomas.<sup>5</sup> Once the polyposis phenotype is confirmed a referral should be made to the colorectal surgical team to plan an elective resection, either a total colectomy with ileorectal anastomosis or a restorative proctocolectomy with pouch formation.<sup>5</sup> The usual timing of these procedures is in the late teenage years or early adulthood. Any residual rectal mucosa requires lifelong surveillance. Upper gastrointestinal malignancies, particularly duodenal and ampullary adenocarcinoma, are

important extra-colonic manifestations of FAP. Thus, annual upper gastrointestinal endoscopy particularly side viewing duodenoscopy is advisable following the development of colorectal disease.<sup>5</sup> Colonoscopy is preferred to sigmoidoscopy in AFAP given the potential for relative distal sparing. Chromoendoscopy is an especially valuable adjunct for AFAP screening and surveillance.

### **MUTYH-associated polyposis**

*MUTYH*-associated neoplasia is an autosomal recessive cause of multiple colorectal adenomas and cancer. Its phenotype is often similar to AFAP, although more severe colorectal disease (>100 adenomas) can occur.<sup>7,8</sup> *MUTYH* is a DNA glycosylase which helps to repair mispaired bases that develop following oxidative DNA damage, and thus protects against mutations in important CRC genes such as *APC* and *K-ras*.<sup>3,8</sup> The *MUTYH* missense mutations Y165C and G382D both impair the enzymatic activity of *MUTYH*, and together account for about 80% of mutant alleles in northern European populations.<sup>3</sup> Biallelic mutations in *MUTYH* confer a 93-fold increased risk of CRC, with almost complete penetrance by 60 years of age.<sup>9,10</sup> Biallelic *MUTYH* mutations appear to be particularly common in patients diagnosed with 15-100 colorectal adenomas without discernable heritable *APC* mutations. In one series 29% of this group had biallelic *MUTYH* mutations.<sup>7</sup> MAP is also associated with extracolonic manifestations including duodenal polyposis.<sup>3</sup>

In patients satisfying the colorectal criteria for at least AFAP, but without evidence of dominant inheritance, *MUTYH* testing should occur in concert with *APC*. In the setting of dominant inheritance of polyposis, however, *MUTYH* should only be performed once *APC* mutation is excluded. Patients with confirmed biallelic *MUTYH* mutations should be managed as for AFAP, with colonoscopic and upper gastrointestinal surveillance, until colectomy is necessitated on the basis of colorectal adenoma burden.<sup>5</sup> Given that MAP is a recessive disorder, genetic testing is offered to siblings, and carrier status of spouse and children is occasionally offered following genetic counselling. The ideal management of patients identified with only one *MUTYH* mutation, however, is uncertain. It is unclear whether these individuals are at significantly heightened risk for CRC. One approach is to consider patients with a monoallelic mutation as having 'at or slightly above average risk' for CRC and offer biennial faecal occult blood testing from the age of 50 years, with flexible sigmoidoscopy every 5 years. Alternatively, offering 5 yearly colonoscopy from the age of 50 years, as for patients 'at moderately increased risk', is another reasonable approach. For patients with monoallelic *MUTYH* mutation identified because of multiple colorectal adenomas, it is appropriate for the clinical phenotype to guide surveillance (see Management of Epithelial Polyps, in The Cancer Council Australia guidelines).<sup>5</sup> We have recently considered this contentious question in some detail.<sup>11</sup>

Several conventional non-steroidal anti-inflammatory drugs, aspirin and COX2-selective inhibitor agents exert an adenoma attenuation effect in both sporadic adenoma and FAP.<sup>12-15</sup> But the benefits of chemoprevention beyond standard care are uncertain at this time.

### **Box 1. Management guidelines for patients with multiple colorectal adenomas**

#### **Diagnosis of AFAP or FAP:**

Local criteria vary, but the current Familial Cancer Unit (SA) criteria for AFAP is the detection of at least 20 colorectal adenomas (can be metachronous) or  $\geq 5$  adenomas in patients <60 years, with a personal history of, or a first- or second-degree relative with, CRC or adenoma with high-grade dysplasia also before 60 years.

#### **Refer to clinical genetics service:**

If there is an autosomal dominant history of colorectal neoplasia then genetic testing will begin with *APC*. If no suggestive family history then *APC* and *MUTYH* testing will be performed concomitantly. *APC* testing can be stopped if biallelic *MUTYH* mutations are discovered.

#### **If an informative mutation is discovered in:**

***APC*** – genetic testing for this mutation should be offered to all first degree relatives following genetic counselling.

***MUTYH*** – genetic testing should be offered to the siblings, and possibly to the spouse and children to clarify carrier status.

#### **If no informative mutations are found then:**

**First degree relatives of patient with AFAP or FAP** – should undergo colonoscopic or flexible sigmoidoscopic screening, respectively, as described in the text. If no colorectal adenomas have developed by age 35 years, then annual surveillance can be extended out to every 3 years, and if still no adenomas by 55 years, then return to population based screening.<sup>5</sup>

#### **Authors:**

**Dr Daniel L Worthley** – Conjoint Gastroenterology Laboratory, Queensland Institute of Medical Research, Brisbane, QLD.

**Dr Lara Lipton** – Familial Bowel Cancer Clinic, Royal Melbourne Hospital, Melbourne, VIC.

References available upon request to The Cancer Genetics Education Project Officer on 08 8291 4269 or [genetics@cancersa.org.au](mailto:genetics@cancersa.org.au)

# Familial Cancer Unit update

## Change in patient selection criteria for BRCA gene studies

The Familial Cancer Unit is being referred more patients than ever before. We are grateful for the opportunity to provide a service to our clients, their families and their referring clinicians.

We are now seeing a broader range of breast/ovarian cancer families, from multi-case early onset breast/ovarian cancer, to late-onset breast/ovarian cancer with fewer family members affected. This has led to an overall decline in the pick-up rate of a BRCA mutation (from 40% in 1995 to around 12% in 2007) most likely because a BRCA mutation is not often identified in late-onset breast cancer families.

Due to the expense of BRCA testing (approx \$2000/patient) and the fact that patient management is often unchanged in the event that a BRCA mutation is **not** identified, there has been a need to review the way we select patients for BRCA gene studies.

A reliable method of identifying women with familial breast/ovarian cancer who are likely to carry an identifiable BRCA mutation has been the subject of intense investigation over the past decade. A clinical scoring system has been developed in Manchester, UK (J Med Genet 2004;41:474-480) which, when applied to our data, has proven to be quite efficient. It reduced overall test volume by 40% with only a 6% reduction in the number of BRCA mutations identified.

**As a result, from October 2007 we commenced using the Manchester scoring system to select patients for BRCA gene studies.**

It should be emphasised that not being selected for BRCA gene studies does not necessarily alter the diagnosis of familial breast cancer. We are still keen to provide genetic counselling, confirmation of family history and on-going surveillance updates for these families. We are simply limiting testing to patients whose familial breast/ovarian cancer is most likely to be attributed to an identifiable BRCA mutation.

In addition there is growing recognition that women with high-grade, serous papillary ovarian cancer (or primary peritoneal cancer) frequently carry a BRCA mutation (approx 15-25%) regardless of age of onset or family history.

**As a result, from October 2007 we commenced a trial of offering BRCA gene studies to any woman with high-grade serous papillary ovarian cancer (or primary peritoneal cancer) irrespective of age or family history.**

These changes represent the most efficient way to select patients for BRCA gene studies in SA at the present time, but there is still much to be learnt and as such these arrangements should be considered an interim response.

For more information please contact Dr Graeme Suthers, Head of the Familial Cancer Unit on 08 8161 6995 or [graeme.suthers@cywhs.sa.gov.au](mailto:graeme.suthers@cywhs.sa.gov.au)

## Resource update

**\*\*NEW exciting resource\*\* Genetics in family medicine: The Australian handbook for general practitioners** (Biotechnology Australia 2007). The 'Cancer in the family' section can be accessed at [www.gpgenetics.edu.au/05/05\\_index.html](http://www.gpgenetics.edu.au/05/05_index.html) and provides info on GP's role and familial cancer syndromes.

**The Cancer Council Helpline 13 11 20** is now available from 8.30am to 8.00pm Monday to Friday. In response to consumer demand, The Cancer Council SA is trialling extended Helpline hours until the end of the year. The trained nurse counsellors can provide information and support, and can be reached on **13 11 20** for the cost of a local call.

**Clinical update – ovarian cancer** is a National Breast Cancer Centre (NBCC) publication for health professionals. [www.ovariancancerprogram.org.au/ocu](http://www.ovariancancerprogram.org.au/ocu) Issue 1 examines: Salpingo-oophorectomy and risk of ovarian cancer in women with a BRCA1 or BRCA2 mutation.

**NEW on-line breast cancer risk calculator** – a new NBCC initiative that can be completed in a few minutes. Gives the facts about risk factors for breast cancer and provides useful information about lifestyle changes that may reduce risk. Access through the NBCC website [www.nbcc.org.au](http://www.nbcc.org.au)

The Clinical Oncological Society of Australia (**COSA**) has **launched a new look website**. Members can log-in and access a range of resources and a forum from each of the twenty one cancer professional groups (including the Familial Cancer group). Access via [www.cosa.org.au](http://www.cosa.org.au)

# DNA banking in familial cancer

For technical reasons, genetic testing to identify the mutation responsible for a family's history of cancer must usually be initiated on a sample from an affected family member. But it is not unusual for the only living affected person in the family to be seriously ill with cancer. This is not the best time to be offering genetic assessment and counselling prior to getting informed consent and collecting a DNA sample for genetic testing. The patient and family usually have other priorities. But if the issue of genetic testing is deferred, the patient may have died before the family is ready to address genetic matters and so the opportunity for getting that key DNA sample may have been lost.

If you are confronted with such a situation, please bear in mind the possibility of banking DNA. A blood sample (10mL in EDTA) can be collected from the patient and forwarded to the IMVS (Molecular Pathology) or FMC (Genetic Pathology) with the usual pathology request form, clinical details, and a request for DNA banking. This sample will not be tested but will simply be stored. There is no requirement for detailed genetic counselling and written consent at this stage as the DNA is only being stored for possible future use.

The laboratories are happy to receive and bank such samples. There is no guarantee that such samples will be tested in the future and any testing would ONLY be done following appropriate counselling and consent of the next of kin.

For some patients, being able to potentially provide genetic information for their relatives without having to tackle significant emotional issues in the short term can be very satisfying.

For more information about **banking DNA samples from patients with familial cancer** please contact the Familial Cancer Unit on 08 8161 6995.

# Staff update

## The Cancer Council SA

Kirsty Stallard is the new Cancer Genetics Education Project Officer at The Cancer Council SA. Kirsty has a background in Medical Science and an Honours degree in Molecular Cell Biology. Her role is to develop, implement and evaluate strategies for enhancing the knowledge of cancer genetics in the public and professional communities.



## Go green

If you prefer to receive the Cancer Genetics Gazette electronically please email your request to [genetics@cancersa.org.au](mailto:genetics@cancersa.org.au)

## Feedback?

If you have any feedback from this edition or suggestions for future editions please send them to the Cancer Genetics Education Project Officer at [genetics@cancersa.org.au](mailto:genetics@cancersa.org.au)

Editorial responsibility for this Newsletter is taken by:

Dr Graeme Suthers  
Head, Familial Cancer Unit  
SA Clinical Genetics Service  
Women's & Children's Hospital  
72 King William Street  
North Adelaide SA 5006

Printing and distribution of this newsletter is sponsored by the SA Familial Cancer Service and The Cancer Council SA.