

Cancer Genetics Gazette



This gazette is sent to you from the Familial Cancer Unit. It aims to provide specialist clinicians with up-to-date information about developments in cancer genetics.

Issue2 November 2005

Surveillance following prophylactic surgery to reduce the risk of cancer

Prophylactic surgery to reduce the risk of cancer is one of the options available to people at high genetic risk of developing familial breast, ovarian, or bowel cancer. This strategy is very effective, but the remaining risk of developing cancer in the specific tissue is not necessarily eliminated. Should such patients continue to have regular cancer surveillance? Or is such surveillance unwarranted and likely to cause unnecessary anxiety?

For the patients and doctors involved, this is not an abstract debate but an important practical issue. As yet, there are no data or guidelines to help us so we have asked some local experts to provide their views on the management of such patients. They are:

Dr David Walsh
Department of Surgery
The Queen Elizabeth Hospital

Dr John Miller
Gynaecological Oncologist
Calvary Hospital

Mr James Moore
Head Colorectal Surgery
Royal Adelaide Hospital

Familial breast cancer, no mutation

A 42 year-old woman has a strong family history of breast cancer. Genetic studies in an affected relative have failed to identify the causative mutation and so genetic testing is not available to determine whether this woman carries the putative mutation responsible for breast cancer in this family. Nonetheless, she was so concerned about her risk of developing breast cancer that she had bilateral prophylactic mastectomies without reconstruction at the age of 40. What long-term breast cancer surveillance should she be offered?

This woman's decision to have prophylactic mastectomies suggests she will have strong views on her future management. Anxiety and an unwillingness to undergo long-term surveillance may have been factors in her decision to have prophylactic surgery.

However, she should be informed of her probable breast cancer risk and a surveillance plan could be utilised.

Recent data from the PROSE study (2004), indicates that bilateral prophylactic mastectomy reduces the risk of breast cancer in women with BRCA1/2 mutations by approximately 90%. It is important that this woman is informed of this significant risk reduction, that she may not have inherited the putative mutation and that mastectomy does not eliminate the possibility of breast cancer. The upper incidence of breast cancer in high

risk/BRCA families is around an 80% lifetime occurrence. A 90% reduction in risk from prophylactic mastectomy for such women means a lifetime incidence of 8% or 1 in 12 women (compared to an Australian average of 1 in 11). Hence, this woman has reduced her risk to just less than the average population risk. If nipple or skin preserving mastectomies were performed then this risk may theoretically be higher, likewise if premalignant changes were present in the histology of her breast tissues, her risk could be expected to be greater.

My advice would be for this woman to perform monthly self examinations (chest wall, axillae and neck). Mammography is not of use after mastectomy, but I would offer annual ultrasound examination of her chest wall flaps and axillae. The potential for an increased risk of ovarian and other cancers, if she is carrying an as yet undetected genetic mutation also needs to be considered. Her family should be closely reviewed. Gynaecological and GI surveillance for this woman may be just as important as following up her breast cancer risk.

Dr David Walsh

Familial breast/ovarian cancer, BRCA1 mutation

A 35 year-old woman with a BRCA1 mutation has elected to have bilateral prophylactic mastectomies with reconstruction, bilateral oophorectomies with hormone replacement therapy, and a hysterectomy. What long-term breast cancer surveillance should she be offered? What long-term gynaecological cancer surveillance should she be offered?

My advice would not change whether or not there was mutation, if the patient was compliant.

Dr David Walsh

Gynaecological surveillance

Prophylactic BSO decreases the risk of ovarian cancer by 96% in BRCA1 Carriers (Prevention and Observation of Surgical Endpoints Study PROSE). At the time of her surgery there is a small (3-8%) risk of a Stage 1 ovarian cancer being found therefore there needs to be thorough histological evaluation of the specimen.

She still has a small (~1% or less) risk of developing primary peritoneal cancer which behaves and is treated in a similar fashion to ovarian cancer. There is no proven screening test for this condition, but she could be offered annual CA125 measurements on the understanding that there is no evidence that this alters her risk of developing, or her prognosis from, primary peritoneal cancer. She should be counselled that if she has abdominal symptoms that persist for >1 month they should be investigated – however symptoms such as distension and bloating usually indicate that the cancer is already advanced and hence outcome not affected.

If the cervix is removed at the time of hysterectomy and no dysplasia is found (and there is no PH of dysplasia), she would only need vault smears if new symptoms warranted it.

Recruitment is presently under way in NSW and Victoria for a Study (USGOG199) investigating risk reducing surgery and screening in women at increased risk of ovarian cancer.

Dr John Miller

HNPCC, no mutation identified

A 32 year-old man with colon cancer and a family history of hereditary non-polyposis colorectal cancer has a total colectomy as part of the surgical management of his cancer. His cancer exhibits microsatellite instability (the molecular hallmark of HNPCC) but no familial mutation can be identified. What long-term colorectal cancer surveillance should he be offered? What other cancer surveillance should he be offered?

Total colectomy as surgical management for an HNPCC associated colorectal cancer involves the preservation of the rectum and an ileorectal anastomosis. There is an appreciable incidence of rectal cancer in the retained rectum over time, (approximately 12% at 20 years) and as such the remaining colorectal mucosa requires surveillance. This can be carried out by sigmoidoscopy (flexible or rigid) as only 15 cm of rectum should remain. Whilst evidence to support other cancer screening is not available, current recommendations would suggest annual urine cytology, biennial upper endoscopy and upper abdominal / renal ultrasound would be reasonable. The use of ultrasound may be tempered by the need for interval CT scanning in the followup of his CRC. The importance of prompt investigation of new symptoms cannot be overstated.

Mr James Moore

HNPCC, MSH2 mutation identified

A 45 year old woman with endometrial cancer, a family history of colorectal and ovarian cancers, and a documented mutation in the MSH2 gene (a DNA mismatch repair gene) has a total hysterectomy but retains her ovaries. What long-

term colorectal cancer surveillance should she be offered? What gynaecological cancer surveillance should she be offered? What other cancer surveillance should she be offered?

Several important issues arise in this situation.

- 1. In the presence of a documented MSH2 mutation, this woman has a 70-80% lifetime risk of developing CRC. She should undergo full colonoscopy prior to her gynaecologic surgery (hopefully she has already been in a screening programme). Given the lifetime risks above, prophylactic total colectomy and ileorectal anastomosis at the time of her hysterectomy should be discussed. I would not recommend prophylactic proctocolectomy (either with or without ileoanal pouch construction). If, after appropriate counselling, she decides against prophylactic colectomy, then annual colonoscopy should be recommended as CRC screening. Faecal occult blood testing has no role.*
- 2. I am surprised that the scenario suggests that this lady will or has undergone total hysterectomy but retains her ovaries. Bilateral salpingo-oophorectomy would normally be recommended as part of surgical treatment of endometrial cancer, her family history includes ovarian cancer and she has roughly 20% chance of developing ovarian cancer on the basis of her mutation.*
- 3. Other cancer surveillance should include suggest annual urine cytology, biennial upper endoscopy and upper abdominal/ renal ultrasound. The use of mammography should probably be along the lines for average risk individuals.*

Mr James Moore

Gynaecological surveillance

The recommended treatment for endometrial cancer includes removal of the ovaries (as they might be sites for occult metastases) and hence I would advise BSO. This is particularly so in this lady who has a MSH2 mutation as she has an increased lifetime risk (9-12%) of developing ovarian cancer.

If she still elects to retain her ovaries I would offer 6 or 12 monthly CA125 measurements and transvaginal US to screen for ovarian cancer. However, there is no evidence that screening in women at increased genetic risk is effective in detecting tumours at sufficiently early stage to affect prognosis. (*Journal of Clinical Oncology* Aug 2005). The PPV of an abnormal US and raised CA125 in detecting ovarian cancer is only ~26%, and the high false positive rate leads to unnecessary surgery in a number of women. If she was retaining her ovaries for hormonal function I would offer laparoscopic BSO once she became menopausal. Once again she would be encouraged to report any persisting abdominal symptoms.

The routine follow up of women who have been diagnosed with a gynaecological cancer (in this case endometrial) is 3 monthly review for 2 years, then 6 monthly to 5 years and annually thereafter. Review involves history and examination with directed investigations. The role of vault smears is still slightly controversial but most would recommend they be done in a woman with a PH of uterine cancer.

No prospective study shows any survival advantage in patients who have routine follow up compared to review as required. However, follow up also has a role in early detection of recurrence or treatment complications, quality assurance and data collection and possible psychological support for patients, (even though it is appreciated that surveillance may cause more

anxiety than reassurance in some patients).

Dr John Miller

Cancer Genetics Education Resources

A national cancer genetics education resource directory can be found on the following National Cancer Control Initiative website:

<http://www.nccci.org.au/CGERD/index.htm>

One of the resources listed in this directory is the website of the *National Coalition for Health Professionals Education in Genetics*.

<http://www.nchpeg.org/>

Established in 1996 by the American Medical Association, the American Nurses Association, and the National Human Genome Research Institute, the National Coalition for Health Professional Education in Genetics (NCHPEG) is an organization committed to an effort to promote health professional education and access to information about advances in human genetics.

Do you wish to receive other cancer genetics newsletters?

The Gene Pool (*cancer genetics newsletter for GPs*)

Gene Trek newsletter (*for clients of the Familial Cancer Unit*)

Do you wish to receive The Cancer Genetics Gazette electronically?

Contact:

Clara Tait

Tel: (08) 8291 4153

Fax: (08) 8291 4268

Email: ctait@cancersa.org.au