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SYDNEY WOMEN'S ENDOSURGERY CENTRE

Sydney Women's Endosurgery Centre

What's new in Gynaecology?

Hereditary Cancers in Women by Dr David Rosen

The lifetime risk of Breast cancer for a woman in Australia is 1:10-11 (9-10%) whilst for Ovarian cancer it is more like 1:100 (1%). *This* risk is independant of external factors. For a small group of Australian woman however these risks increase dramatically—those who carry the genes for familial cancer syndromes.

- BRCA $_1$
- BRCA $_2$
- HNPCC, amongst others

Carriers of the Breast cancer susceptibility gene 1 have a 36-46% increase lifetime risk of ovarian cancer, whilst for BRCA 2 this increased risk is 10-27%. Yet most women who suffer breast or ovarian cancer are NOT gene positive, and a strong family history (see box) is suspicious for but not diagnostic of a gene mutation. Thus about 5% of all Breast cancers and 10% of all ovarian cancers can be explained by inherited genetic defects.

What are these genes?
BRCA 1 and 2 are tumour suppressor genes. They are inherited by an autosomal dominant process from a parent where the absence or defect in one of these genes affects the repair of damaged DNA and eventually leads to cancer. For some reason, breast and ovarian cancers (in women) are the major forms of resulting tumours. Homozygosity (ie, a defective gene from both parents) is lethal to an embryo for BRCA 1, and is associated with multiple types of inherited anemias for the BRCA 2 homozygote.

Who is at risk?
Three groups exist;
1. Those with a known gene positive family—what should they do?
2. Those with a family history (see box)
3. Those affected with breast / ovarian cancer who want to know what is the risk to their family members.

Let's look at the general population of women, those who would fall into group 2.

High risk of breast/ovarian cancer

- **Assessed as high risk of the other type (ie Breast or ovary)**
- **3 or more close relatives on one side of the family with breast or ovarian cancer OR**
- **2 or more close relatives on same side of family with B or O Ca. + one of:**
  - **more relatives with B / O Ca.**
  - **Breast Ca. before age 40**
  - **bilateral Breast ca.**
  - **Ashkenazi Jewish heritage***
  - **Breast Ca. In a male relative**

OR

- **3 or more close relatives on same side of the family with colorectal, uterine, gastric cancers (HNPCC) OR**
- **A known gene +ve family member**

* + one close blood relative with ovarian cancer

The National Breast Cancer Centre has divided women in to three categories;
1. Average risk—95% of women
2. Moderate risk—4%
3. High risk— 1% (see table above)

Those at average risk have no family history *or* one first degree relative with breast cancer diagnosed after age 50 *or* one second degree relative at any age or 2 second degree relatives on the same side of the family diagnosed after age 50. As a guide to general practitioners, women in the low and moderate risk groups should have routine Breast and Ovarian screening tests such as second annual mammography after age 50 and regular bimanual pelvic examinations.

Who should be tested?
Testing for the inherited mutations is costly and time consuming. Consequently it is recommended that only those with a high risk be tested. If they fall into the categories outlined above (see box), referral to a family cancer centre

Referral to a family cancer centre is appropriate. There, blood from the affected close relative (those who have had breast/ ovarian cancer) is tested to look for a faulty gene. If detected, other blood relatives can have a predictive test for this defect. Some groups are at high risk e.g. Ashkenazi (European origin) Jews carry a 2% risk in any individual of BRCA 1/2 mutation, therefore they may be offered testing without an affected family member.

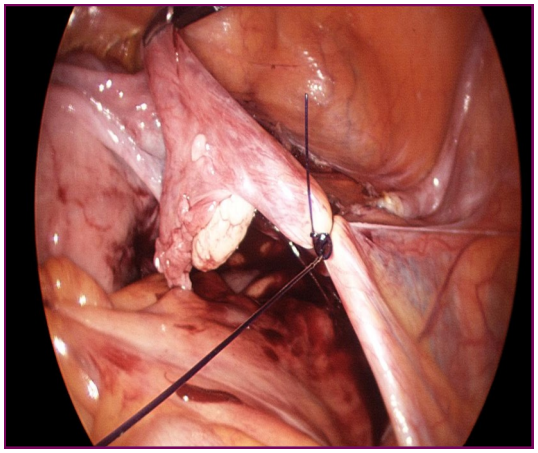

Fig 1. tube and ovary on the right pelvic sidewall. Note the wide separation of the ligature around the supplying vessels from the ovarian tissue

What about women already affected by Breast /Ovarian cancer?

1. Check the histology and mutation analysis to determine her risk of cancer in the other breast / ovary.
2. Tumour type—serous papillary and endometrioid ovarian tumours are more likely to be associated with BRCA mutations (not mucinous or borderline types).
3. Women with ovarian cancer who have previously had breast cancer have a 42% chance of being BRCA+ve.
4. History of primary fallopian tube cancer carries a 40% risk of BRCA mutation, whilst primary peritoneal cancer has a 20% association.

For those women with a history of Breast cancer, a definite history of ovarian cancer in a relative, with or without a diagnosed genetic mutation, is an indication for prophylactic risk-reducing bilateral salpingooophorectomy (rrBSO) as not all mutations are as yet identifiable.

Unaffected women who discover they are carriers—what are the options?

This is one of the most difficult questions and will of course depend greatly on the patients personal circumstances and stage of life. Information is the cornerstone of informed decision making and consultation with a genetic counselor, gynaecologist and/or breast surgeon will create many questions but hopefully seek to answer more.

Such counseling should encompass;

- Fertility history or desires
- Patient fears and expectations
- Discussion regarding future oestrogen replacement therapy, risks and benefits
- The risks and benefits of prophylactic surgery

Accordingly, the treatment options for an asymptomatic woman who learns that she is gene positive are -

1. Watch—no intervention, regular surveillance as for the general population
2. Screen—regular transvaginal ultrasound and ovarian tumour markers
3. have not been shown to provide any benefit
4. OCP—there is a potential 40-50% reduction in the risk of ovarian cancer in ever users of the OCP for greater than 5 years, the effect lasting for up to 20 years after cessation of use. Unfortunately it is unknown as to whether this benefit extends to BRCA cases.
5. Tubal ligation—may reduce the risk of ovarian cancer with the BRCA mutation by up to 60%
6. Risk reducing salpingooophorectomy (RRSO) - for a woman whose family is complete, bilateral removal of the tubes and ovaries has been shown to have the greatest effect in reducing the risk of future malignancies;

• 80-90% reduction in ovarian cancer

• 50% reduction in breast cancer (70% if < 40 years of age, 40% if

• BUT, there is a 4-10% risk of occult malignancy being found in the re-

6. Hysterectomy—removal of the uterus should *always* be considered when bilateral salpingooophorectomy is performed. Despite the operation being slightly more complicated, the benefits far outweigh the risks. Namely;

- Use of postoperative oestrogen replacement is facilitated, without the need to use progesterone to protect the endometrium, This reduces the small associated risk of breast cancer with combined HRT, and is especially important in the younger woman who will immediately go into the menopause after surgical removal of her ovaries.
- Use of tamoxifen in the future without the fear of associated endometrial malignancy.
- In patients with the HNPCC gene, hysterectomy is advocated as they have an increased risk of endometrial cancer.

How does this practice fit in?
Women with a hereditary cancer gene do NOT have cancer. They are undergoing a prophylactic procedure to reduce their (increased) risk of developing a malignancy in the future. Consequently the surgery does not have to be performed by an oncologist. Indeed for a woman who is not sick having a procedure to remove otherwise healthy organs, the most minimal intervention with the least discomfort and lifestyle limitation is indicated.

That is where the expert laparoscopic surgeons have a role. We specialize in benign gynaecological surgery performing Total laparoscopic hysterectomy with or without removal of the ovaries on a routine weekly basis. Laparoscopic surgery has been shown, in countless studies, to have a significantly lower inpatient stay and faster return to normal activity than laparotomy. For a woman with hereditary cancer genes, the important surgical considerations are;

1. Peritoneal washings—because of the 4-10% risk of undiagnosed malignancy being already present, staging techniques for possible ovarian cancer should be performed

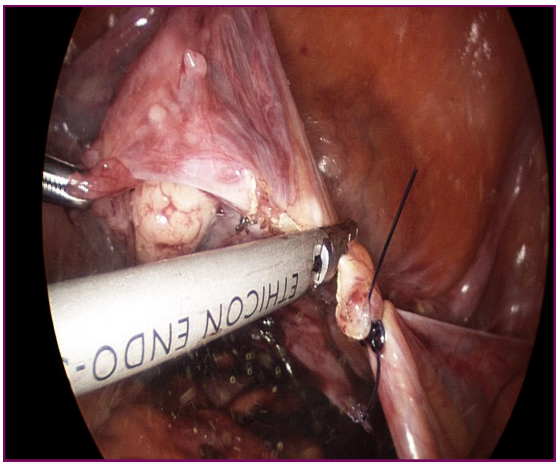

Fig 2. Ligating the infundibulopelvic ligaments using the Laparoscopic coagulating shears

2. Be certain that no tubal or ovarian tissue is left within the body (see figure 2) - expert dissection is made to isolate and ligate the infundibulopelvic ligaments high on the pelvic brim away from the adnexae.

3. Vaginal hysterectomy is not suitable when washings and complete oophorectomy without ovarian remnants is desired.

We welcome the opportunity to discuss these matters further with you or your patients.

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