Advice about familial aspects of breast cancer and epithelial ovarian cancer

A guide for health professionals

This guide is general guide for appropriate practice to be followed subject to the health professional's judgment of each case. It is designed to provide information to assist decisions made by health professionals and their patients. The guide is based on the best available evidence or consensus opinion of experts where evidence does not exist at the date of publication.

This guide has five parts:

References:

1. Adapted with permission from: The National Breast and Ovarian Cancer Centre, Level 1 Suite 103/355 Crown St Surry Hills NSW 2010 Australia Tel: +61293579400 Fax:+61293579477 Free call 1800624973 **National Breast and Ovarian Cancer Centre 2010** www.nbocc.org.au; and
2. **Malaysian Clinical Practice Guidelines** on Management of Breast Cancer 2010; and
3. **NICE** guidelines on familial breast cancer 2013

ADVICE ABOUT FAMILIAL ASPECTS OF **BREAST CANCER AND OVARIAN CANCER**

Assessing family history

Family history of breast or ovarian cancer can be used to estimate:

- A woman's risk of developing these cancers
- The probability of having an inherited mutation in a known cancer- predisposing gene.

Key factors associated with increased risk include:

- Multiple relatives affected by breast (male or female) or ovarian cancer
- Young age at cancer diagnosis in relatives
- Relatives affected by both breast and ovarian cancer
- Relatives affected with bilateral breast cancer

Taking a family history

Consider relatives on each side of the family separately.

An accurate family history should include:

- Asking the woman about any primary cancer in all 1° (parents, siblings, children) and 2° (aunts, uncles, nieces, nephews, grandparents) relatives on both sides of the family
- Establishing the site and age at diagnosis of the cancer(s)
- Confirming, if possible, reports of cancer in relatives – *a person's knowledge of their family history may be inaccurate*
- Updating the family history regularly – *it may change with time.*

Risk factors for breast and ovarian cancer

The main risk factors for breast and ovarian cancer are

- Being female
- Increasing age
- Family history

Breast cancer

The risk of developing breast cancer is 1 in 20 (4.9%) in Malaysia; 1 in 16 (6.3%) for Chinese women, 1 in 15 (6.5%) for Indian women, and 1 in 26 (3.5%) for Malay women. (National Cancer Registry 2003)

Ovarian cancer

The risk of developing epithelial ovarian cancer is 1 in 167 (0.6%) in Malaysia; 1 in 125 (0.5%) for Chinese women, 1 in 143 (0.8%) for Indian women, and 1 in 200 (0.7%) for Malay women in Malaysia.

Family history does not necessarily imply an inherited genetic cause. However, at least 1% to 5% of breast cancers and up to 15% of all cases of invasive ovarian cancer involves the inheritance of a mutated gene.

The vast majority of affected women do not carry an inherited mutation in a known breast or ovarian cancer-predisposing gene.

Which genes are associated with a predisposition to breast or ovarian cancer?

Women born with a mutation in one of several known genes (see Table 1) have an increased risk of breast and/or ovarian cancer.

There may be other genes, as yet undiscovered, in which mutations are also associated with a risk of breast or ovarian cancer.

The women most likely to have inherited a mutation are those with the strongest family history of breast or ovarian cancer.

Family cancer clinics

In Malaysia, we do plan to develop dedicated family cancer clinics. However, Genetics Clinic, Oncology and Breast Clinics have temporarily taken up this role. The service is offered to any family members, whether or not they have been diagnosed with cancer. After assessing detailed information about a woman's family history of cancer, these clinics provide genetic counselling including:

- Information about a person's risk of developing cancer based on family history and other relevant factors as well as to recommend genetic testing.

Table 1. Genes for which mutations are known to be associated with an inherited predisposition to breast or ovarian cancer and possibly cancer at other sites

Gene	Mutation	Major sites at risk	Risk to age 75 in mutation[c]	Other possible sites with up to 10% lifetime
BRCA1	~1/1000	Breast Ovary	40% - 80%	Prostate
BRCA2	~1/1000	Breast Ovary	40% - 80%	Male breast, prostate, pancreas
Tp53[a]	~1/10,000	Breast Bone or Soft tissue	>50% 10% - 50%	Brain, lung, adrenal gland, haematological and other
Mismatch repair genes (MMR)[b]	~1/1000	Large bowel Uterus	50% - 80% 40%	Ovary, other gastro-intestinal, renal tract

[a] This syndrome is commonly referred to as the Li-Fraumeni syndrome [b]This syndrome is commonly referred to as hereditary non-polyposis colorectal cancer (HNPCC) or Lynch Syndrome [c] There is a wide range of risk associated with mutations in these genes

GENETIC TESTING

It is possible to detect mutations in some cancer-predisposing genes. Some mutations may not be detected using current technology. Testing involves first searching for a gene mutation, usually in a blood sample from an affected family member. Should a mutation be found, testing may then be offered to other adult relatives who may carry the same mutation. Genetic testing is offered **only with pre- and post-test counselling** to discuss the limitations, potential benefits, and possible consequences.

Criteria for Genetic Testing

Women whose family history is associated with an increased risk for deleterious mutations in *BRCA1*, *BRCA2* or *TP53* genes should be referred for genetic counselling and evaluation for genetic testing.

This includes individuals with breast or ovarian cancer that have affected blood relatives with any one of the following family history patterns (these individuals should be from the same side of family):

BRCA 1 or BRCA2

- Triple negative breast cancer <50 years old*
- Medullary carcinoma*
- 3 or more first or second degree relatives on the same side of family with breast or ovarian cancer any age; or
- 2 or more first or second degree relatives on the same side of family with breast cancer, 1 of whom was diagnosed ≤ age 50 years old; or
- 2 or more first or second degree relatives on the same side of family with ovarian cancer at any age; or
- 1 first degree relative with breast cancer diagnosed ≤ age 40 years old; or
- 1 first degree relative with both breast and ovarian cancer at any age; or
- 1 first degree relative with bilateral breast cancer at any age; or
- 1 first degree relative with male breast cancer; or
- Family history of breast cancer in combination with other *BRCA*-related cancers, such as pancreas, prostate and oesophageal cancers on the same side of family; or

TP53

- Family history of early onset breast cancer in combination with other *TP53*-related cancers such as sarcomas and multiple cases of childhood cancers on the same of family.

Refer to:

1) Genetic Clinic, Hospital Kuala Lumpur.
Tel: +603-2615 5555 ext 7062 Fax: 03-2691 2853
Email: klinikalgenetik.hkl@moh.gov.my

2) Cancer Research Malaysia
Tel: +603 5639 1874, Fax: +603 5639 1875
Email: info@cancerresearch.my

3) University Malaya Medical Centre (UMMC)
Risk Assessment Clinic (RAC), Breast Clinic, UMMC
Tel: +60379493642

The following categorization applies to women without breast or ovarian cancer:

ADVICE ABOUT FAMILIAL ASPECTS OF BREAST CANCER

CATEGORIES OF RISK	MANAGEMENT
1. At or slightly above average risk	
Covers more than 95% of the female population As a group, risk of breast cancer up to age 75 is about 1 in 20. • No confirmed family history of breast cancer • One 1° relative diagnosed with breast cancer at age 50 or older • One 2° relative diagnosed with breast cancer at any age • Two 2° relatives on the same side of the family diagnosed with breast cancer at age 50 or older • Two 1° or 2° relatives diagnosed with breast cancer, at age 50 or older, but on different sides of the family (i.e. one on each side of the family).	• At present risk models that are used in western populations cannot be applied to local patients. • Advice risk is similar to that of the general population. • Reassure that 19 out of 20 women in this group will not develop breast cancer. • Inform that breast cancer risk increases with age. • Discuss modifiable risk factors for breast cancer. • Encourage all women to be aware of the normal look and feel of their breasts and promptly report persistent or unusual changes to their GP. • Investigate women with symptoms using the Triple Assessment.
2. Moderately increased risk	
• One 1° relative diagnosed with breast cancer before the age of 50 (without the additional features of the potentially high-risk group – see category 3) • Two 1° relatives, on the same side of the family, diagnosed with breast cancer (without the additional features of the potentially high-risk group – see category 3) • Two 2° relatives, on the same side of the family, diagnosed with breast cancer, at least one before the age of 50, (without the additional features of the potentially high- risk group – see category 3).	• Clarify risk. • Advise that there is a moderately increased risk of developing breast cancer • Reassure that most of the women in this group will not develop breast cancer • Advise the woman to attend regular screening mammograms • Advise that a more precise risk assessment and management plan is available in specialist cancer clinic. **Additional screening** • Annual mammograms from age 40 may be recommended if the woman has a first degree relative < 50 years diagnosed with breast cancer. Referral to a family cancer clinic may be appropriate • Annual mammograms are not recommended for women with a single relative diagnosed > 50 years, as there is no clear evidence of benefit • In women over 35 years of age, consider the use of medication, such as tamoxifen or if postmenopausal raloxifene, to reduce risk of developing breast cancer. This requires careful assessment of risk and benefits in the individual case by an experienced medi cal professional • Discuss modifiable risk factors for breast cancer • Encourage all women to be aware of the normal look and feel of their breasts and promptly report persistent or unusual changes to their GP • Investigate women with symptoms using the Triple Assessment.
3. Potentially high risk	

• Individual risk may be higher or lower if genetic test results are known (refer table 1).
  • Women who are at potentially high risk of ovarian cancer (See page 5)
  • Two 1° or 2° relatives on one side of the family diagnosed with breast or ovarian cancer plus one or more of the following 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
  • 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 on the same side of the family with sarcoma (bone/soft tissue) at age 45 or younger
• Member of a family in which the presence of a high-risk breast cancer gene mutation has been established.
	• Clarify risk.
	• Advise that although there is a high or potentially high risk of developing breast cancer, and perhaps other cancers, many wo men in this group will not develop breast cancer
	• Advise referral to a family cancer clinic cancer specialist clinic for risk assessment, possible genetic testing and management plan. Discuss risk reduction strategies which may include:
	  ➢ Risk-reducing surgery
	  ➢ Consideration of the use of medication, such as tamoxifen or raloxifene, to reduce risk of developing breast cancer.
	• Ongoing screening strategies which may include:
	  ➢ Regular clinical breast examination
	  ➢ Annual breast imaging with mammography, MRI or ultrasound
	  ➢ Consideration of ovarian cancer risk (see page 5).
	• Discuss modifiable risk factors for breast cancer
	• Encourage all women to be aware of the normal look and feel of their breasts and promptly report persistent or unusual changes to their GP
	• Investigate women with symptoms using the Triple Assessment.

The following categorization applies to women <u>without</u> breast or ovarian cancer:

ADVICE ABOUT FAMILIAL ASPECTS OF <u>OVARIAN CANCER</u>

CATEGORIES OF RISK	MANAGEMENT
1. At moderately increased risk	
Covers more than 99% of the female population • No confirmed family history of epithelial ovarian cancer • One 1° or 2° relative diagnosed with ovarian cancer at any age (provided the family does not have any additional cases of breast cancer) • Two 1° or 2° relatives diagnosed with ovarian cancer, but on different sides of the family (i.e. one on each side of the family).	• Advise that risk is similar to the rest of the population • Reassure that more than 9 out of 10 women in this group will not develop ovarian cancer • Inform that evidence does not support screening women in this group with ultrasound or CA125 Note: If a woman reports a family history of epithelial ovarian cancer between the ages of 35 and 50, consider referral to a family cancer clinic for risk assessment, possible genetic testing and management plan.
2. Potentially high risk	

Covers less than 1% of the female population
 	
As a group, risk of ovarian cancer up to age 75 is between 1 in 30 and 1 in 2. This risk is more than 3 times the population average. Individual risk may be higher or lower if genetic test results are known.
 	
• Women who are at high risk of breast cancer due to a gene fault
• One 1° or 2° relative with ovarian cancer at any age, and another with breast cancer before the age of 50, where the women are 1° or 2° relatives of each other
• Two 1° or 2° relatives on the same side of the family diagnosed with epithelial ovarian cancer eg. serous carcinoma, especially if one or more of the following features occurs 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**
  • **Breast cancer in a male relative.**
 	
• Three or more 1° or 2° degree relatives on the same side of the family diagnosed with a family history suggestive of Lynch Syndrome (or HNPCC) e.g. colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer, and cancers involving the renal tract
 	
• Member of a family in which the presence of a high-risk ovarian cancer gene mutation has been established.
	• Advice there is a high/potentially high risk of developing ovarian cancer, and perhaps other cancers such as breast,bowel or endometrial cancer
	• Advise referral cancer specialist centre for risk assessment, possible genetic testing and management plan
	• Discuss risk management strategies:
	  ➢ Risk-reducing surgery. The most effective risk-reducing strategy for ovarian cancer is bilateral salpingo-oophorectomy (BSO). (NB: BSO also reduces breast cancer risk when done before age 40)
	  ➢ Chemoprevention (use of medication to prevent ovarian cancer). Use of the oral contraceptive pill (OCP) may be an option for pre- menopausal women who choose not to have risk-reducing surgery. The impact on breast cancer risk for mutation carriers is unclear.
	
	• Ovarian cancer screening is not recommended for women at high or potentially high risk. Evidence shows that ultrasound or CA125, singly or in combination, is not effective at detecting early ovarian cancer
	• Discuss screening relevant to other cancers (e.g. Attending for clinical breast examination, mammography for breast cancer; or other screening, if the family cancer history is consistent with Lynch Syndrome)

Breast cancer screening for high risk unaffected individuals

Summary of recommendations on screening for women with no personal history of breast cancer. (NICE Guidelines for familial breast cancer 2013)

Age	Moderate risk	High risk				
	Moderate risk of breast cancer[1]	**High risk of breast cancer (But with a 30% or lower probability of being a *BRCA* or *TP53* carrier)**[2]	**Untested but greater than 30% *BRCA* carrier probability**[3]	**Known *BRCA1* or *BRCA2* mutation**	**Untested but greater than 30% *TP53* carrier probability**[4]	**Known *TP53* mutation**
20-29	Do not offer mammography	Do not offer mammography	Do not offer mammography	Do not offer mammography	Do not offer mammography	Do not offer mammogram
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI	Annual MRI	Annual MRI
30-39	Do not offer mammography	Consider annual mammography	Annual MRI and consider annual mammography	Annual MRI and consider annual mammography	Do not offer mammography	Do not offer mammogram
	Do not offer MRI	Do not offer MRI			Annual MRI	Annual MRI
40-49	Annual mammography	Annual mammography	Annual mammography and annual MRI	Annual mammography and annual MRI	Do not offer mammography	Do not offer mammogram
	Do not offer MRI	Do not offer MRI			Annual MRI	Annual MRI
50-59	Consider annual mammography	Annual mammography	Annual mammography	Annual mammography	Mammography as part of the population screening	Do not offer mammogram
	Do not offer MRI	Do not offer MRI	Do not offer MRI unless dense breast pattern	Do not offer MRI unless dense breast pattern	Do not offer MRI unless dense breast pattern	Consider annual MRI
60-69	Mammography as part of the population screening	Mammography as part of the population screening programme	Mammography as part of the population screening programme	Annual mammography	Mammography as part of the population screening	Do not offer mammogram
	Do not offer MRI	Do not offer MRI	Do not offer MRI unless dense breast pattern	Do not offer MRI unless dense breast pattern	Do not offer MRI unless dense breast pattern	Consider annual MRI
70+	Mammography as part of the population screening programme	Mammography as part of the population screening programme	Mammography as part of the population screening programme	Mammography as part of the population screening programme	Mammography as part of the population screening programme	Do not offer mammogram

[1] Lifetime risk of developing breast cancer is at least 17% but less than 30%. [2] Lifetime risk of developing breast cancer is at least 30%. High risk group includes rare conditions that carry an increased risk of breast cancer, such as Peutz-Jegher syndrome, (*STK11*), Cowden (*PTEN*), familial diffuse gastric cancer (E-Cadherin). [3] Surveillance recommendations for this group reflect the fact that women who at first assessment had 30% or greater *BRCA* carrier probability and reach 60 years of age without developing breast or ovarian cancer will now have a lower than 30% carrier probability and should no longer be offered MRI surveillance. [4] Surveillance recommendations for this group reflect the fact that women who at first assessment had 30% or greater *TP53* carrier probability and reach 50 years of age without developing breast cancer or any other *TP53*-related malignancy will now have a lower than 30% carrier probability and should no longer be offered MRI surveillance.

Guideline for risk management in affected *BRCA* carriers (those who had developed breast and or ovarian cancer)

- Managing future risk will depend on cancer stage at diagnosis. Risk management would apply to early cancer with no evidence of distant disease. Developing new cancers should be weighed against risk of relapse of initial cancer. The risk of contralateral breast cancer is 3% in Malaysia (unpublished).
- Risk of future cancers are counselled similar to unaffected individuals if the individual has not developed the site specific cancer.
- Risk of future cancers in affected individuals is currently unknown and we depend on risk figures published from non-Malaysian studies.
- Shared decision making should be practiced for all risk management strategies.
- A re-staging CT-Thorax, abdomen and pelvis is required before planning any invasive procedures. A multidisciplinary approach is required with participation of the surgeon, oncologist, psycho-oncologist or equivalent and genetics service team in making recommendations.

RISK-REDUCING STRATEGIES AND EVIDENCES	SCHEDULE
Intensive surveillance ***Breast cancer screening***	• Annual screening should be done from age of 30 years with both MRI and mammography as it is more effective than mammography alone (Grade B) • Regular clinical breast examination
Ovarian cancer screening • Intensive screening for ovarian cancer in *BRCA* carriers is not supported because of the current limitations in sensitivity and specificity of transvaginal ultrasounds (TVUS) and/or measurement of serum CA125 level.	• Risk reducing salpingo-oophorectomy (RRSO) is therefore strongly recommended to BRCA1/2 mutation carriers once childbearing is complete. • Annual screening via blood test CA125 and TVUS if no surgical intervention planned
Chemoprevention ***Tamoxifen or Raloxifene*** • Significantly reduced the overall risk of breast cancer, but this effect was observed only for oestrogen receptor-positive but not oestrogen receptor-negative tumours. • Tamoxifen may reduce the risk for breast cancer for *BRCA2* carriers but not for *BRCA1* carriers, and may also reduce the risk of contralateral breast cancer in *BRCA* carriers. • Use of tamoxifen associated with several adverse effects, including increased in thromboembolic events, stroke, endometrial cancer, gynaecological problems and cataracts • Use of Raloxifene also has thromboembolic events but has no increased risk of endometrial cancer and cataracts ***Oral contraceptives*** • Reduced ovarian cancer in the general population and in *BRCA1* and *BRCA2* mutation carriers • It may not be associated with an increased risk of breast cancer.	• Tamoxifen 20mg at least 5 years. Raloxifene 60mg at least 5 years. • Raloxifene in postmenopausal women only. • Patients on chemoprevention does not eliminate breast cancer, hence this is practised with intensive surveillance.
Risk-reducing surgeries ***Risk-reducing mastectomy*** • Reduce 85-100% risk of breast cancer • Contralateral risk reducing mastectomy reduces 85-100% risk of breast cancer and improved overall survival • ***Risk-reducing salpingo-oophorectomy*** • Reduced risk for ovarian cancer by 85 - 100% and breast cancer by 53- 68%. • Associated with an improvement of overall survival	• Bilateral or contralateral risk-reducing mastectomy should be offered to women with deleterious mutations in *BRCA1/BRCA2* with no specific recommended age. (Grade B) • Pre-menopausal high risk women are the most likely to benefit from risk-reducing salpingo-oophorectomy, but also the most likely to experience side effects from surgery, including the loss of fertility, loss of sexual function and increased osteoporosis. • Thus, risk-reducing salpingo-oophorectomy is advised after completion of childbearing and from the age of 35 years to 39 years old.

Grades of recommendation A: At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population. B: Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency or results; or evidence extrapolated from meta-analysis, systematic review, or RCT. C: Evidence from expert committee report, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality.