Protocol 3
BRCA mutation carrier guidelines
Frequently asked questions

Last updated: 09/02/2015

Q: How accurate are the remaining lifetime and 5 year breast cancer risks in the table?
These figures are risks for an "average carrier" and they **do not** represent a definitive risk for an individual carrier. The data provided are taken from a data set implemented in BOADICEA for a cohort of randomly ascertained mutation carriers of unknown family history. The figures have been averaged and condensed to present the data in a practical format for use in clinic. The averaged figures represent the best approximate remaining lifetime and 5 year risk figures for an individual of a given age.

The principal aim of the figures is to aid discussion for patients who are considering surgery. Many carriers find remaining lifetime risks and/or more qualitative discussions most helpful, and the 5 year risk figures in the table need only be utilised if helpful.

Q: Why is the range of lifetime risk of breast cancer so broad and different to the figures in the table?
The range for lifetime breast cancer risk, 60-90% for BRCA1 and 45-85% for BRCA2, reflects the range of risk figures derived from population-based studies and family-based studies.

The lower figure in the range is taken from population-based studies in which BRCA1 and BRCA2 carriers were identified in cases unselected for family history. The upper figure in the range is taken from penetrance figures from large, multiple case families with breast and/or ovarian cancer.

Most families seen in Genetics have some family history, but only a small proportion have a strong family history comparable to the multiple case families used in the original linkage studies. The risks provided in the tables are risks for an average carrier, taken from a dataset in BOADICEA, and are likely to be broadly reflective of the majority of families currently seen in Genetics.

Q: How can I give a 10 year risk of breast cancer to a patient?
Consecutive 5 year risks can be summed to give 10 year risks. For example, a 31 year old BRCA1 carrier has an estimated 5 year breast cancer risk of 5% and a 10 year risk of 15% (5%+10%).

Q: Why can't I sum the figures to give >10 year risks?
The 5 year risks are conditional on being unaffected at the age from which the risk is being given. They thus become progressively less accurate as one adds successive 5 year risks. For example the 25 year risk for an unaffected 31 year old BRCA1 carrier is estimated to be 42% from BOADICEA rather than 55% (the sum of the 5 year risks: 5+10+10+15+15%). If for decision making it is important to give a longer risk one should say "assuming you are still unaffected in 10 years time, your risk of breast cancer over the following 10 years would be 25%" (10 + 15%). However, it is much preferable to use the remaining lifetime risk to illustrate the longer-term risk and the 5 /10 year risks to guide management over the next decade.

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Q: Why doesn't bilateral risk-reducing mastectomy reduce risk by 100%?
Bilateral risk-reducing mastectomy has been shown to reduce the risk of breast cancer by approximately 90-95%. Following bilateral mastectomy, breast cancer may still occur in the chest wall and therefore the risk reduction is not 100%. Mammographic surveillance is not required following bilateral mastectomy, but women should be made aware of the small possibility of chest wall disease, and to see their doctor if they discover a chest wall lump.

Q: What surgical options are there for bilateral risk-reducing mastectomy?
All carriers should be offered the opportunity to discuss risk-reducing mastectomy with an experienced breast surgeon and should be made aware that there are a number of options for breast reconstruction following surgery. http://www.macmillan.org.uk/ offers simple advice on the different types of breast reconstruction after risk-reducing surgery. All carriers are entitled to more than one surgical opinion. Women can also be referred to a psychologist if discussions regarding impact on body image would aid decision-making.

Q: Why are the contralateral breast cancer risk figures not broken down into different age groups?
There is still considerable uncertainty regarding the risk of contralateral breast cancer, particularly at different ages. The available data are inconsistent and all have limitations. In part this is because multiple factors, such as the mode of treatment for the first cancer, the age of the first cancer and whether oophorectomy has been performed, impacts on contralateral risk and can be difficult to appropriately correct for in studies. Therefore we have provided overall estimates which are broadly consistent between studies.

- Lifetime contralateral risk is approximately 50% for both BRCA1 and BRCA2
- For BRCA1 carriers the 5 year risk is estimated to be ~10%.
- For BRCA2 carriers the 5 year risk is estimated to be 5-10%

Q: What is the risk of ipsilateral breast cancer?
It is similarly difficult to accurately estimate the risk of ipsilateral breast cancer and there is considerable variation in published figures, not least because it can be difficult to distinguish between recurrence and new primaries. Surgery for the first breast cancer (mastectomy or breast conserving) will have a major impact.

If a considerable amount of breast tissue remains then the risk may be more similar to the contralateral risk, but if little tissue remains and radiotherapy/chemotherapy has been given then the risk is reported to be more similar to that of individuals with sporadic cancer.

Q: When should I discuss chemoprevention with BRCA carriers?
Chemoprevention can be discussed and offered to BRCA2 carriers. Chemoprevention should not be offered to BRCA1 carriers, due to the potential increased risk of ER negative breast cancer.

Q: What benefits of chemoprevention should I discuss?
Women should be made aware that chemoprevention reduces the overall number of ER positive breast cancer cases that develop, but does not have any impact on mortality.

Q: What major side effects of chemoprevention should I discuss?
Tamoxifen use is associated with a small increased risk of endometrial cancer and venous thromboembolism.

Q: What minor side effects of chemoprevention should I discuss?
Common side effects include menopausal symptoms such as hot flushes and vaginal discharge or dryness. Some patients can experience mild nausea, weight gain and muscle

and joint pains. Many women find that the side effects of chemoprevention are significant enough to stop taking the medication. Studies report that about 1 in 5 women will stop taking chemoprevention due to side effects.

Q: Are there any contraindications to chemoprevention?

- Tamoxifen should not be taken if there is a personal or family history of blood clots or a family history of endometrial cancer.
- Tamoxifen and raloxifene should not be taken with HRT (Hormone Replacement Therapy) or the contraceptive pill.
- Tamoxifen or raloxifene can also interfere with the action of other drugs, so it is important for the prescribing Doctor to take a drug history
- Tamoxifen and raloxifene should not be taken if a woman is trying to conceive.

Q: At what age can chemoprevention be started?
Chemoprevention should not be started prior to age 35.

Q: How long can chemoprevention be taken?
A maximum of 5 years is recommended.

Q: Who will prescribe chemoprevention?
Following discussion in a Specialist Genetics or Family history clinic, a letter can be sent to the patients GP to prescribe chemoprevention, should the patient wish to pursue this.

Q: Why are there not tables for remaining lifetime risk and 5 year risk of ovarian cancer?
Robust figures are not currently available. For most women the timing of risk-reducing bilateral salpingo-oophorectomy (BSO) is determined by child-bearing rather than 5 year risks. The following figures are appropriate to use for counselling purposes;

- The majority of lifetime risk is conferred after age 40 for BRCA1 carriers - Approximate 10 year risk 10-15% for rest of lifetime.
- The majority of lifetime risk is conferred after age 50 for BRCA2 carriers - Approximate 10 year risk 5-10% for rest of lifetime.

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Q: Why do we recommend risk-reducing bilateral salpingo-oophorectomy?
Bilateral salpingo-oophorectomy (BSO) is generally well tolerated as a laparoscopic procedure. Ovarian cancer has a higher mortality than breast cancer and there is no proven, efficacious form of surveillance (see below).

Prophylactic BSO has been demonstrated to reduce ovarian cancer risk in BRCA carriers by up to 96%.

Prophylactic BSO is also associated with a reduction in lifetime breast cancer risk of approximately 50%. It is presumed that the risk reduction is facilitated by undergoing prophylactic BSO premenopausally, although the exact relationship between age of surgery and risk reduction is not known.

Q: At what age should women undertake risk-reducing bilateral salpingo-oophorectomy?
For BRCA carriers, who have not had risk-reducing bilateral mastectomy and who have completed their families it is appropriate to consider BSO from 40 onwards, as this will maximise the benefit in terms of ovarian and breast cancer risk reduction.

The benefit in terms of ovarian cancer risk reduction applies at whatever age BSO is undertaken; the benefit in breast cancer risk reduction will be facilitated by undertaking BSO premenopausally.

For BRCA1 carriers who have had risk-reducing bilateral mastectomy, BSO should still be considered from age 40 onwards, due to the associated ovarian cancer risk in their 40's.

For BRCA2 carriers who have had risk-reducing bilateral mastectomy it is reasonable to delay BSO until age 45, as there will be no additional benefit of breast cancer risk reduction.

Obviously there are also many personal factors that may influence this decision and which should be taken into consideration. For example, sometimes women wish to consider bilateral salpingo-oophorectomy earlier because there have been younger cases within their family.

Q: What are the disadvantages of risk-reducing bilateral salpingo-oophorectomy?
The primary negative consequence of BSO in premenopausal women is a premature surgical menopause which may result in menopausal symptoms such as hot flushes, vaginal dryness, sexual dysfunction, sleep and cognitive disturbances. Premature menopause may also be associated with increased risk of osteoporosis and heart disease in later life.

HRT should be used to minimise these effects and should be started in women who have not had breast cancer from time of surgery until 50 years (the approximate time of the natural menopause).

Carriers should be made aware of the small risk of peritoneal serous papillary carcinoma that remains following BSO.

Q: Does HRT use after risk-reducing bilateral salpingo-oophorectomy affect the reduction in breast cancer risk?
Short-term HRT use does not negate the protective effect of BSO on subsequent breast cancer risk in BRCA carriers and should be used from surgery until 50 years, unless there are contraindications.

Q: Can HRT be given after risk-reducing bilateral salpingo-oophorectomy to women who have had breast cancer?
HRT is generally avoided in women who have had breast cancer, although it can be considered in some circumstances. A decision to give HRT in this context must only be made after thorough discussions with the oncologist.

Q: What ovarian surveillance is available to carriers?
Ovarian surveillance is not recommended for BRCA carriers, as no ovarian surveillance modality (including trans-vaginal ultrasound or CA-125 measurement), has demonstrated improved survival for BRCA carriers.

Q: What advice should be given to carriers regarding the use of the oral contraceptive pill (OCP)?
The available data suggests that the effects of the OCP in BRCA carriers are likely similar to those in the general population, in whom the OCP appears to confer a protective effect for ovarian cancer and endometrial cancer but long term use may slightly increase breast and cervical cancer risk.

In BRCA carriers, increasing duration of OCP use is associated with an increasing reduction in ovarian cancer risk. However the OCP can not be used as a chemopreventative agent for

ovarian cancer due to the association of longer term use (5 years or more), with a slightly increased risk of breast cancer.

Use of the OCP is thus not contraindicated in BRCA carriers. If carriers enquire about OCP use, the above should be articulated. The decision to take the OCP will largely be a personal one and carriers may feel that in the short term the OCP provides the most appropriate form of contraception for them.

Q: What types of breast and ovarian cancers do BRCA carriers get?
Breast and ovarian cancers can be of any histological subtype but there are a number of recognised associations.

In BRCA1 carriers the most frequent sub-type of breast cancer is the basal type, usually negative for oestrogen, progesterone and HER2 receptors. These are sometimes called triple-negative tumours.

Ovarian cancers in both BRCA1 and BRCA2 carriers are predominantly epithelial serous papillary carcinomas (~60-90%) with epithelial endometrioid histology accounting for most of the remaining cases.

Q: What are the cancer risks for male BRCA2 carriers?
BRCA2 carriers have an increased lifetime risk of male breast cancer (~5-10%). No breast surveillance is recommended for male carriers but patients should be advised about breast self-awareness and to see their GP should they develop a lump. There is also a small increased lifetime risk of prostate cancer (~25% by age 80 years).

Q: What are the cancer risks for male BRCA1 carriers?
Male breast and prostate cancer risks are only slightly increased above population risk and any discussions of these risks must clearly articulate this. No surveillance for breast or prostate cancer is recommended.

Q: Do I need to discuss any other cancers with BRCA carriers?
Small excesses of a number of cancers other than breast and ovarian (e.g. pancreatic and gastric cancers and melanomas) have been observed in BRCA1 and BRCA2 carriers, but their risks are similar to that of the general population. Therefore the risk of other cancers usually does not warrant discussion unless there is a notable family history of cancers other than breast, ovarian and prostate.

Due to only marginal increased relative risks of these cancers, cumulative lifetime risks remain low; and no surveillance is recommended. Some research programmes offer enrolment to BRCA families to evaluate the efficacy of surveillance programmes e.g. EUROPAC are evaluating the potential of pancreatic cancer surveillance and will accept referrals of families with a BRCA2 mutation and at least one documented case of pancreatic cancer.

Q: What ongoing follow-up do BRCA carriers require?
This will depend on the individual circumstances. In the period after the test results, multiple appointments may be required whilst the management plan is being formulated. Conversely, for a woman who has had bilateral risk-reducing mastectomy and BSO no routine follow-up will likely be required. All BRCA carriers should be logged on the Carrier Register.

Q: What recommendations should be made to individuals at 50% risk of a BRCA mutation?

The benefits of predictive testing should be clearly articulated to all individuals who are at 50% risk. Testing informs management and treatment options. Breast surveillance begins at age 30 years and ideally predictive testing should be undertaken by this time so that the appropriate management protocol can be implemented.

NICE and NHSBSP recommend that individuals with 50% risk of a BRCA1 or BRCA2 mutation are eligible for MRI; however this may not be possible in practice due to limited MRI capacity. Priority will be given to confirmed carriers of TP53, BRCA1 or BRCA2 mutations.

Q: How should I manage an individual in whom a predictive test is negative?
A negative predictive test is when an individual is found to not carry the mutation that has been shown to be responsible for the breast/ovarian cancers in their family. On the basis of current knowledge such individuals should be returned to population breast surveillance, as per the NHSBSP. No ovarian or prostate surveillance is recommended**.**

Q: How do I manage a BRCA negative family?
Please see Protocol 1.

Q: How do I manage a BRCA variant?
Reports from TGLclinical should always provide clarity about the management recommendations of variants. External reports may not provide this. If you are unclear about the management of a variant email: vus@icr.ac.uk. Ensure that the lab report and a summary of the clinical history are included in the email.

Glossary
BC – Breast Cancer
OC – Ovarian Cancer
NICE – National Institute for Clinical Excellence
NHSBSP – National Health Service Breast Screening Programme
BOADICEA – Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
ER – oestrogen receptor
PR - progesterone receptor
HRT – Hormone replacement therapy
BSO – Bilateral salpingo-oophorectomy
EUROPAC – European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer