Breast cancer - managing family history - Management

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When and how do I take a family history?

- Take a family history of breast cancer when the woman expresses concerns about her family history, or if concerns arise during the consultation (for example the woman has breast symptoms, or concerns relating to use of hormone replacement therapy or oral contraceptives).
- Ask whether a faulty gene has been identified in the family.
- Ask whether any first- or second-degree relatives (on the maternal or paternal side of the family) have had breast cancer (see Table 1).
  - To be considered relevant, all affected relatives must be on the same side of the family and be blood relatives of the woman and of each other.
  - Paternal history is relevant if there are two or more relatives diagnosed with breast cancer (or related cancer) on the woman's father's side of the family.
  - Try to gather detailed information (such as the age when diagnosed, certainty of the diagnosis).
- If there is a positive first- or second-degree family history, also determine:
  - Whether other cancers have occurred in the family, specifically:
  - Ovarian cancer.
  - Sarcoma at younger than 45 years of age.
  - Glioma, or childhood adrenal cortical cancer.
  - Complicated patterns of multiple cancers at a young age.
  - If any family member has had bilateral breast cancer (each breast cancer has the same count-value for risk as one relative, that is, the family member would count twice: once for each breast with cancer).
  - If there is Jewish ancestry.

- Where appropriate encourage the woman to discuss the family history with relatives.

Table 1. Family history.

Degree of relative	Relative
First-degree relative	Mother, father, daughter, son, sister, brother
Second-degree relative	Grandparents, grandchildren, aunt, uncle, niece, nephew, half-sister, half-brother
Third-degree relative	Great-grandparents, great-grandchildren, great-aunt, great-uncle, first-cousin, grand-nephew, grand-niece

Basis for recommendation

- These recommendations are based on the guideline from the National Institute for Health and Clinical Excellence (NICE), *Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care* [NICE, 2006a]. NICE commissioned the National Collaborating Centre for Primary Care to produce the evidence review and develop the clinical guidelines [McIntosh et al, 2004].

- NICE recommends that if the woman has breast symptoms, or has concerns about relatives with breast cancer, that a first- and second-degree family history should be taken. A family history allows a classification of risk to be made that will direct further management decisions.

- NICE found:

  - Four observational studies that assessed the accuracy of the family history provided by women (735 women with breast cancer and 251 women without breast cancer) and concluded that family histories were generally reliable.
  - A review of five case studies that showed the importance of verifying the history.
  - One longitudinal, qualitative study of 46 women attending a UK genetics clinic for familial breast/ovarian cancer that found that poor communication between family members may impede the collection of family history.

How do I assess a woman's risk of breast cancer and need for referral?

The following recommendations represent minimum criteria for referral. Locally-developed guidelines may be available and should be followed.

- **If a faulty gene has been identified in the family,** offer direct referral to a specialist genetics service (if the person has not already been seen by such a service).
- **If there is no first- or second-degree maternal or paternal family history of breast cancer,** manage in primary care by offering appropriate information and reassurance.
- **If there is a first- or second-degree family history,** but of only one relative who developed breast cancer after 40 years of age, manage in primary care.
- **If there is a first- or second-degree family history of breast cancer affecting a relative 40 years of age or younger, or more than one relative:**
  - Offer referral to secondary care if the woman is likely to be *at more than moderate risk* of developing breast cancer (see Table 1).
  - Otherwise:
  - If the woman is likely to be *at moderate risk* (see Table 1), and the woman is 40–49 years of age, offer referral.
  - If the woman is likely to be *at moderate risk* (see Table 1), but the woman is younger than 40–49 years of age, inform her that she will not generally be offered additional mammography. However, if she requests risk counselling/management or wants to be considered for prevention trials, seek advice from secondary care regarding her level of risk and whether referral is appropriate.
  - If the woman is likely to be *at less than moderate risk* (see Table 1), manage in primary care.
  - If the woman has a positive first- or second-degree family history and does not fulfil any of the above criteria for referral but there is a history of unusual cancers in the family (see Unusual cancers), there is a paternal history of breast cancer, or there is Jewish ancestry, seek advice from secondary care regarding her level of risk and whether referral is indicated.

- **Consider referring, or discussing with secondary or tertiary care, those women who are particularly concerned about their risk of breast cancer but in whom it is impossible to assess risk accurately,** such as:

  - Where there is doubt over the diagnosis of breast cancer in their relatives or the age at which the cancer occurred.
  - Those women with a small family (for example who have no sisters or aunts).
  - Women who were adopted and do not know their family history.

Table 1. Referral criteria from primary to secondary care.

Women likely to be at more than moderate risk	Women likely to be at moderate risk
Female breast cancers only One first-degree and one second-degree relative diagnosed at younger than an average of 50 years of age* Two first-degree relatives diagnosed at younger than an average of 50 years of age* Three or more first- or second-degree relatives diagnosed at any age	**Female breast cancers only** One first-degree relative diagnosed before 40 years of age One first-degree relative *plus* one second-degree relative diagnosed after 50 years of age Two first-degree relatives diagnosed after an average of 50 years of age*
Male breast cancer One first-degree male relative diagnosed at any age	
Bilateral breast cancer One first-degree relative where the first primary was diagnosed at younger than 50 years of age. For bilateral breast cancer, each breast has the same count value as one relative	
Breast and ovarian cancer One first- or second-degree relative with ovarian cancer diagnosed at any age *plus* one first- or second-degree relative with breast cancer at any age (one should be a first-degree relative)	

*To calculate an average age, add the ages of all people together and divide by the number of people.
Data from: [NICE, 2006b]

Unusual cancers

- Bilateral breast cancer.
- Male breast cancer.

- Ovarian cancer.
- Sarcoma at younger than 45 years of age.
- Glioma or childhood adrenal cortical cancer.
- Complicated patterns of multiple cancers at a young age.

Basis for recommendation

- These recommendations are based on the quick reference guide from the National Institute for Health and Clinical Excellence [NICE, 2006b], and the guideline *Familial breast cancer: the classification and care of women ar risk of familial breast cancer in primary, secondary and tertiary care* [NICE, 2006a].

What advice can I give regarding risk reduction and lifestyle?

- Recommend breast awareness to all women.
  - Explain the principles of breast awareness. This is a process whereby the woman becomes familiar with her own breasts by looking and feeling and reporting promptly any changes. Changes could include: discomfort or pain; lumps, thickening, or bumpy areas; nipple changes or discharge; or changes in the appearance of the breast, such as in the shape or the presence of dimpling of the skin.
  - For more information, see the NHS Cancer Screening Programme information on Breast awareness (pdf).
- Encourage attendance at the local breast-screening programme for women 50 years of age and older. From 2012 the NHS breast screening programme will be extended to cover women 47–73 years of age. Women who are older than the eligible age range will still be able to self-refer, as at present.
- Discuss known (potentially modifiable) risk factors for breast cancer.
  - An increased risk of breast cancer is associated with:
  - Alcohol consumption.

- Being postmenopausal and overweight.
- Older age of first birth.
- A reduced risk of breast cancer is associated with:
- Moderate physical activity.
- Breastfeeding.
- Increased number of births.

- Smoking is not thought to be a risk factor for breast cancer, but smokers should be encouraged to quit because of the other health benefits (for further information see the CKS topic on Smoking cessation).

Basis for recommendation

- These recommendations are based on the guideline from the National Institute for Health and Clinical Excellence (NICE), *Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care* [NICE, 2006a]. NICE commissioned the National Collaborating Centre for Primary Care to produce the evidence review and develop the clinical guidelines [McIntosh et al, 2004].

Breast self-examination

- NICE recommends that all women at increased risk of breast cancer should be breast aware [NICE, 2006a]. There is evidence from a Cochrane systematic review that screening (by either regular self-examination or clinical examination) is not beneficial. Therefore, current advice is for women to be 'aware' of any changes in their breasts and seek early advice if they detect any changes.

Breast screening

- The Cancer Reform Strategy sets a clear direction for cancer service development between 2007 and 2012. It outlines plans to extend the breast screening programme to nine screening rounds for women 47–73 years of age. Over 400,000 more women will be screened each year as a result [DH, 2007].

Alcohol

- NICE examined five meta-analyses, one systematic review, and one cohort study and concluded that there is no good evidence to suggest that the risk from drinking alcohol is any different for women with a family history of breast cancer compared with women as a whole. Women who drink a moderate amount of alcohol have a slightly higher risk of breast cancer than those who abstain.

- A subsequent case-controlled study investigated women with BRCA1 or BRCA2 mutations who had a history of breast cancer (cases) or did not (controls) [McGuire et al, 2006]. In the BRCA1 group there were 195 cases and 302 controls, and in the BRCA2 group there were 128 cases and 179 controls. No positive association was found between alcohol intake and the risk of breast cancer in women with either BRAC1 or BRCA2.

Weight

- NICE found evidence that a high body mass index is associated with a clinically significant increase in postmenopausal breast cancer risk in the general population.

Menstrual/reproductive factors

- After reviewing the available limited evidence, NICE concluded that the:

  - Risk of breast cancer is increased by:
  - Early menarche.
  - Older age at first birth.
  - A late menopause (55 years of age or older).
  - Risk of breast cancer is decreased by:
  - Pregnancy, with increasing numbers of pregnancies conferring greater risk reduction.

- However, in women who carry BRCA1 or BRCA2, an analysis of data from a cohort study of 1187 women with a BRCA1 mutation and 414 women with a BRCA2 mutation found no association between the age of either the menarche or the menopause on breast cancer risk [Chang-Claude et al, 2007].

- In women who carry mutations in BRCA1 or BRCA2, there is conflicting evidence about whether younger age at first birth alters the risk of breast cancer. However there is evidence that increased parity offers protection.

  - In a case-controlled study, 1816 women with breast cancer who carried either the BRCA1 mutation (1405 women) or the BRCA2 mutation (411 women) were matched with women who carried the BRCA1 or BRCA2 mutation but who did not have breast cancer [Kotsopoulos et al, 2007]. An early first full-term birth did not appear to confer protection (OR 1.0, 95% CI 0.98 to 1.03).

  - In a case-controlled study, 457 women who carried either a BRCA1 or BRCA2 mutation and who had breast cancer were compared with women carrying the same mutations who had not developed breast cancer [Antoniou et al, 2006]:

  - Parous women older than 40 years of age were at lower risk.

  - The risk of breast cancer increased with the age of the first live birth.

  - A retrospective cohort study of 1601 women with a BRCA1 or BRCA2 who were included in the International BRCA1/2 Carrier Cohort Study found that [Andrieu et al, 2006]:

  - A statistically significant decrease in the risk of breast cancer was associated with an increasing number of full-term pregnancies. The risk was reduced by 14% (95% CI 6 to 22) for each additional birth. This was the same in women with either a BRCA1 or BRCA2 mutation and was restricted to women older than 40 years of age.

  - In BRCA2-mutation carriers, a late first birth was associated with an increased risk of breast cancer compared with first birth before 20 years of age.

  - In BRCA1-mutation carriers, first birth at 30 years of age or later was associated with a reduced risk of breast cancer compared with first birth before 20 years of age.

Physical activity

- NICE reviewed the evidence and concluded that moderate physical exercise is associated with a decreased risk of breast cancer in the general population.

Breastfeeding

- After reviewing the available evidence (one meta-analysis, one systematic review, and a collaborative group re-analysis of individual data from 47 epidemiological studies) NICE concluded that breastfeeding confers a small protective effect on the risk of breast cancer.

Smoking

- There are many health benefits from stopping smoking. However, there is no good association between smoking and the risk of breast cancer (although results of studies have not been consistent).
- A recent case-controlled study compared 2538 women with breast cancer (1920 with a BRCA1 mutation and 618 with a BRCA2 mutation) with an equal number of women with a mutation but no breast cancer [Ginsburg et al, 2009]. There was no increased risk of breast cancer in current smokers (odds ratio [OR] 0.95, 95% CI 0.81 to 1.12) but there was a possible increased risk among BRCA1 carriers who were past smokers (OR 1.27, 95% CI 1.06 to 1.5).

When should I offer follow up?

- Inform all women concerned about developing breast cancer that their risk may change with age and with changes in their family history.
- Advise women younger than 40 years of age with any of the following to return for referral upon reaching 40 years of age:
  - One first-degree relative diagnosed with breast cancer when younger than 40 years of age.
  - One first-degree and one second-degree relative diagnosed when older than an average of 50 years of age (to calculate the average age, add the ages of both together and divide by two).
  - Two first-degree relatives diagnosed when older than an average of 50 years of age.

- Remind woman older than 50 years of age that they are already eligible for mammographic surveillance.

Basis for recommendation

- These recommendations are based on the guideline from the National Institute for Health and Clinical Excellence (NICE), *Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care* [NICE, 2006a].

What advice should I give about hormonal contraception?

Women with a family history of breast cancer

- The UK Medical Eligibility Criteria (UKMEC) state that a family history of breast cancer is not a contraindication to any form of hormonal contraception or intrauterine device. The following may therefore be used without restriction (UKMEC category 1: a condition for which there is no restriction for the use of the contraceptive method):

  - Combined oral contraceptive (COC).
  - Progestogen-only pill.
  - Depot medroxyprogesterone acetate (Depo-Provera®).
  - Etonogestrel-only implant (Implanon®).
  - The levonorgestrel-releasing intrauterine system (Mirena®).

Women who are known carriers of a gene mutation

- If the woman is a carrier of a known gene mutation associated with breast cancer (for example BRCA1):

  - The COC should generally not be used (UKMEC category 3: the theoretical or proven risks usually outweigh the advantages).
  - The progestogen-only pill, depot medroxyprogesterone acetate (Depot-Provera®), the etonogestrel-only implant (Implanon®), or the levonorgestrel-releasing intrauterine system (Mirena®) may generally be used (UKMEC

category 2: a condition where the advantages of using the method generally outweigh the theoretical or proven risks).

- For further information, see the CKS topic on Contraception.

Basis for recommendation

- These recommendations are based on the UK Medical Eligibility Criteria (UKMEC) for contraceptive use [FFPRHC, 2006] and a guideline from the Faculty of Sexual and Reproductive Healthcare [FSRH, 2007].
- The National Institute for Health and Clinical Excellence (NICE) reviewed the evidence and concluded that [McIntosh et al, 2004]:
  - Consistent evidence is provided by three meta-analyses of case-control and cohort studies, plus one large case-controlled study (4575 women with breast cancer and 4682 women without breast cancer), that the effect of oral contraception on breast cancer risk is similar in women with or without a family history of breast cancer.
  - In women with a BRCA1 mutation, taking the combined oral contraceptive (COC) may increase the risk of breast cancer. However, the evidence for this originates only from a case-control study and a retrospective cohort study, and should be balanced against the lifetime protection against ovarian-cancer associated with the COC.

What advice should I give about hormone replacement therapy?

- Seek specialist advice if the woman is considering hormone replacement treatment (HRT) and fulfils the criteria for specialist assessment of her risk of breast cancer.
- Generally:
  - Inform women who are considering taking, or who are already taking, HRT of the increase in breast cancer risk (associated with the type and duration of treatment).
  - Ensure that oestrogen-only HRT is prescribed if the woman does not have a uterus.

- Keep the dose as low as possible for as short a time as possible.
- Generally, if the woman is at moderate-to-high risk of breast cancer, then HRT should only be given until she reaches 50 years of age.

- For women who have had breast cancer, see the section on Current or previous breast cancer in the CKS topic on Menopause.

Basis for recommendation

- These recommendations are based on the guideline from the National Institute for Health and Clinical Excellence (NICE) [McIntosh et al, 2004] and published expert opinion [Rees and Purdie, 2006].

- NICE reviewed the available evidence and concluded that hormone replacement therapy (HRT) is associated with an increase in the risk of breast cancer.
- The risk seems to be two-fold for women taking combined HRT for 10 years or more, but is small for short-duration use (up to 2 years).
- The risk associated with HRT disappears 5 years after stopping treatment.

- Evidence from a meta-analysis and a large prospective study suggests that women with a family history of breast cancer have the same relative risk increase from use of HRT as the general population.

For further information, see the CKS topic on Menopause.

What is likely to happen in secondary care?

- A more detailed family history will be taken, with a more accurate assessment of risk.
- All women satisfying referral criteria to secondary care (such as those with a moderate-to-high risk of breast cancer) will be offered mammographic surveillance from 40 years of age.
- From 40–49 years of age this will be annually.
- From 50 years of age this will be every 3 years as part of the NHS Breast Screening Programme.

- Individualized strategies will be developed for women 30–39 years of age and older than 50 years of age who:
- Are from families with BRCA1, BRCA2, or TP53 mutations.
- Have an equivalent high risk of breast cancer.
- Women younger than 30 years of age will not be offered mammographic surveillance.

- When mammography is recommended in women younger than 50 years of age, digital mammography should be used in preference to conventional mammography at centres where this is available to NHS Breast Screening Programme standards.
- Women who are thought to be at high risk (that is, a 10-year risk greater than 8% at 40–49 years of age, or a lifetime risk of 30% or greater, or who have a 20% chance of a faulty BRCA1, BRCA2, or TP53 gene) should be referred to a specialist genetics clinic in tertiary care.

Basis for recommendation

- These recommendations are based on the guidelines from the National Institute for Health and Clinical Excellence (NICE) [NICE, 2006a].
- There is uncertainty about the optimum age and frequency of mammographic and magnetic resonance imaging screening because the evidence base is incomplete [NICE, 2006a].

Recommendations for mammographic surveillance

- For women 50–69 years of age, mammographic surveillance has been shown to reduce mortality from breast cancer [National Collaborating Centre for Primary Care, 2006].
- The benefits of mammography in women 30–49 years of age is uncertain. Some evidence suggests a possible benefit in women 40–49 years of age if they have an increased risk; based on this, NICE suggests mammographic screening in this group [NICE, 2006a].
- Mammographic screening in women younger than 40 years of age or older than 69 years of age is not recommended as there is almost no evidence for benefit in this age group. It is known that the density of breast tissue in younger women, particularly those younger than 30 years of age, means that a mammogram is unlikely to be informative [NICE, 2006a]. Surveillance is less

sensitive in younger women, in women with a family history of breast cancer, and in carriers of the BRCA1 or BRCA2 mutation [Kerlikowske et al, 1996; Kerlikowske et al, 2000; Goffin et al, 2001].

- The risk of radiation-induced breast cancer is small compared with the benefits of cancer detection. The margin of benefit over risk is sufficient in women with a family history of breast cancer to support screening from 40 years of age [Law, 1997; Law and Faulkner, 2001].

What is likely to happen in tertiary care?

- Women at high risk of breast cancer (that is, meeting the criteria for a referral to tertiary care) should be offered genetic counselling

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- Provide standardized information beforehand, detailing the process of genetic counselling and genetic testing. Advise the woman that referral to a genetics service may involve the investigation of other relatives with breast cancer, including a histological diagnosis.
- Advise the woman that she will be offered an estimate of her personal risk of breast cancer. She will also be informed about the uncertainties of the estimate regarding the risk of inheriting a predisposing gene, of penetrance, and hence of developing cancer [NICE, 2006a].

- After discussion of the risks and benefits, advise the woman that she may be offered:

- Mammographic or magnetic resonance imaging (MRI) surveillance.
- Genetic testing. If there is greater than a 20% risk of BRCA1, BRCA2, or TP53 mutation in the family and there is an affected relative available, then genetic testing should be offered after two sessions of pre-test counselling. The affected relative is always screened initially.
- Risk-reduction surgery (prophylactic bilateral mastectomy and/or oophorectomy).
- All women considering risk-reduction surgery should have access to a support group and be able to discuss reconstruction options, the effects and

management of early menopause (after oophorectomy), and possible psychosocial and sexual consequences of surgery.

- If risk-reduction surgery is being considered and no mutation has been identified, confirmation of the family history should be sought through medical records, the cancer registry, or death certificates. When it is impossible to verify the family history, agreement should be sought from a multidisciplinary team before proceeding.

Magnetic resonance imaging

- Women who are known to have a genetic mutation should be offered annual magnetic resonance imaging (MRI) surveillance if they are:

- BRCA1- and BRCA2-mutation carriers and 30–49 years of age.
- TP53-mutation carriers and 20 years of age or older.

- MRI surveillance should be offered annually to:

- Women 30–39 years of age who have a 10-year risk of breast cancer greater than 8%.
- Women 40–49 years of age who have a 10-year risk greater than 20%, or a 10-year risk greater than 12% where mammography has shown a dense breast pattern.
- Women 30–49 years of age who have not been tested but have a high chance of carrying a BRCA1 or TP53 mutation if they have:
- A 50% risk of carrying one of these mutations in a tested family.
- A 50% risk of carrying a BRCA1 or TP53 mutation in an untested or inconclusively tested family with at least a 60% chance of carrying a BRCA1 or TP53 mutation (that is a 30% risk of carrying one of these mutations).

Basis for recommendation

- These recommendations are based on the guideline from the National Institute for Health and Clinical Excellence (NICE) [NICE, 2006a].

Recommendations for magnetic resonance imaging surveillance (MRI)

- These recommendations are based on recent evidence showing that [NICE, 2006a]:

  - MRI increases the sensitivity of breast cancer screening, which means that there is the potential to detect breast cancer at an early stage.
  - MRI is more effective than mammography in screening younger women, because of differences in breast tissue density.
  - Therefore, MRI surveillance is now recommended for younger women who are at high risk of breast cancer and who meet certain criteria.

Risk-reduction surgery

- NICE reviewed the available evidence and concluded that [McIntosh et al, 2004]:

  - Mastectomy and/or oophorectomy reduce the risk of breast cancer in women with a family history of breast cancer or with BRCA1 and BRCA2 mutations, but surgery is appropriate for only a small proportion of women from high-risk families.
  - Risk-reducing total mastectomy is associated with fairly high levels of satisfaction and a reduction in both anxiety and psychological morbidity. It will not prevent the development of all breast cancers. There is inconsistent evidence about psychosocial outcomes after oophorectomy.

How is genetic testing carried out?

- Genetic testing is appropriate only for a small number of women from high-risk families and is possible only if there is a living relative with the disease who is willing to be tested.
- Genetic testing is a two-stage process. It begins with a search for a genetic mutation in a relative with cancer to try to identify a mutation in the appropriate genes (BRCA1, BRCA2, and if the pedigree warrants it the TP53 gene as well). It may also be appropriate to test for a less common gene if the clinical features suggest a particular gene such as PTEN (Cowden's syndrome).

- If, in the initial testing of the relative with cancer:

  - A causative mutation is not found: the unaffected woman who initially presented should be informed that genetic testing on her or any other unaffected family member is unlikely to be informative and is not recommended. However, the absence of an identifiable gene fault does not mean that there is definitely not one present (not all gene faults can be identified).
  - A causative mutation is found: a predictive test (family-specific mutation test) is made available to all female blood relatives, including the unaffected woman who initially presented.
  - If the predictive test is negative, the unaffected woman who has been tested should be reassured that a specific causative gene that was found in her relative has not been found in her, and there is no risk of transmitting that particular gene fault to her children. Her risk of breast cancer is the same as that of the general population.
  - If the predictive test is positive, this means that the woman has inherited the gene fault from her relative and her risk of cancer is increased. Each of her children has a 50% risk of inheriting the gene fault.
  - The Department of Health have set the following standards for the time taken for the results of genetic tests to be available:
  - Within 2 weeks, where the potential genetic mutation is already known (such as where another family member has already been tested).
  - Within 8 weeks, for unknown mutations in a large gene.

Basis for recommendation

- These recommendations are based on the guideline from the National Institute for Health and Clinical Excellence (NICE) [NICE, 2006a], and advice from Breakthrough Breast cancer [Breakthrough Breast Cancer, 2009] and CKS expert reviewers.

Genetic testing

- NICE reviewed the available evidence and concluded that [McIntosh et al, 2004]:

  - Uptake of genetic testing is relatively high, indicating the acceptability of such programmes.
  - Most women cope well in the interval between blood sampling and receiving the result.
  - As expected, women found to be carriers of BRCA1/BRCA2 mutations have more psychological morbidity on post-test follow ups than those with a negative result.
  - Face to face counselling and discussion is useful.

Time taken for the results of a genetic test to be available

- These standards have been set by the Department of Health in their white paper *Our inheritance, our future:realising the potential of genetics in the NHS* [DH, 2003].