Familial breast cancer: Evidence Update May 2012

A summary of selected new evidence relevant to NICE clinical guideline 41 ‘The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care’ (2006)
Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE teams. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/breast-cancer). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care. **Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.**
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Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:


This guideline is under review, with an expected publication date of April 2013. Further details about the update to the familial breast cancer guidance are available at: http://guidance.nice.org.uk/CG/Wave25/1

A search was conducted for new evidence published between 1 March 2002 and 10 August 2011. Approximately 2900 pieces of evidence were identified and assessed, of which 23 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

1 NICE-accredited guidance is denoted by the Accreditation Mark🔗
**Key messages**

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages for this Evidence Update. It also indicates the EUAG’s opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance which may be affected, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

<table>
<thead>
<tr>
<th>Key message</th>
<th>Potential change</th>
<th>No change</th>
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<tbody>
<tr>
<td><strong>Approaches to care for all women</strong></td>
<td></td>
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<tr>
<td>• Limited evidence suggests that genetic risk assessment in breast cancer may be associated with positive outcomes for patients irrespective of the type of healthcare professional administering the risk assessment.</td>
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<td>• The perceived risk of developing a heritable cancer may be influenced by personality factors, and does not correlate with the actual risk.</td>
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<tr>
<td>• Interactive educational computer programs may be more effective than standard genetic counselling for increasing knowledge of breast cancer and genetic testing for women at low risk of carrying a BRCA1 or BRCA2 mutation; however genetic counselling is not currently recommended for this patient population.</td>
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<td>• Computer-based patient decision aids for genetic testing in familial breast cancer do not seem to be truly interactive or designed for use by patients. Available decision aids were not developed for use in the UK, and current guidance does not cover interventions to help with communicating risk to patients.</td>
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<td><strong>Care of women in primary care</strong></td>
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<td>• The evidence-base for tools to aid collection of data about family history of breast cancer in primary care is limited.</td>
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<td><strong>Care of women in specialist (secondary and tertiary) care</strong></td>
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<td>• Surveillance with a combination of magnetic resonance imaging (MRI) and mammography may be more sensitive than mammography alone.</td>
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<td>• Testing for genetic mutations in women at high risk of breast cancer, but without confirmed family history of mutations, may be helpful in determining eligibility for MRI surveillance.</td>
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<tr>
<td>• Annual mammography for women at moderate risk of breast cancer seems to reduce predicted mortality from breast cancer compared with historical studies.</td>
<td>✔</td>
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<td>Key message</td>
<td>Effect on guidance</td>
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<tr>
<td>• Genetic testing for BRCA1 or BRCA2 may increase anxiety and distress in the short-term for people who test positive, but this seems to return to pre-testing levels over time.</td>
<td>✓</td>
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<tr>
<td>• Risk-reducing mastectomy and oophorectomy appear to be associated with a reduction in the incidence of breast cancer.</td>
<td>✓</td>
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<tr>
<td>• Evidence suggests that, in women who have not had breast cancer, tamoxifen(^2) may be useful in prevention of hormone-related tumours. Further studies are needed to determine whether chemoprophylaxis is a viable alternative to risk-reducing surgery.</td>
<td>✓</td>
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<tr>
<th>Risk factors</th>
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<tbody>
<tr>
<td>• Uncertainty remains regarding the relationship between the use of oral contraceptives and the risk of breast cancer.</td>
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</table>

\(^2\) Tamoxifen is not recommended for prophylaxis of breast cancer in current guidance, and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.
1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided. Section headings are taken from the guidance.

1.1 Approaches to care for all women

Cancer genetic risk assessment

Sivell et al. (2007) conducted a Cochrane review to assess the effect of genetic risk assessment services on patients at risk from familial breast cancer and analysed three randomised controlled trials (RCTs) with a total of 1251 participants.

The reviewed studies assessed perception of risk, satisfaction and psychological well-being; patients with a previous history of breast cancer or other serious illness were excluded. A meta-analysis of the data was not done because the three studies were heterogeneous with regards to both interventions and outcomes.

Overall, data from the review suggested that cancer genetic risk assessment services alleviate distress, improve accuracy of perceived risk, and increase understanding regarding breast cancer and genetics. The type of healthcare professional administering the risk assessment did not appear to significantly affect the assessed outcomes.

The authors acknowledged that data were too few to draw firm conclusions, and suggested a need for further research. Evidence from this Cochrane review may help with decisions about who should administer genetic counselling and potentially, genetic testing, but is not likely to influence any update to NICE CG41. This Cochrane review was updated after the searches were conducted for this Evidence Update, however the conclusions did not change (see Hilgart et al. 2012).

Key reference

Supporting reference

Factors influencing cancer risk perception in high risk populations

In a systematic review without meta-analysis, Tilburt et al. (2011) characterised factors that may influence the perceived risk of developing cancer for patients at high risk of heritable cancer. The review included 53 studies, of which 34 looked at breast cancer (other studies were of ovarian, colon and prostate cancer). Of all included studies, 37 included women only. The aim of this review was to characterise the existing data for factors that may influence perceived risk of developing cancer for those at high risk of cancer, to form an evidence-based model for use in future research into risk communication.

For patients at high risk of heritable cancer, several clinical, demographic and psychosocial factors associated with perceived risk of developing cancer were identified. In particular, a family history of cancer, and undergoing previous tests and treatments were associated with a higher perception of cancer risk. Furthermore, individual patient beliefs regarding the preventability and severity of cancer, personality factors, and the ability to handle numerical data, as well as distress or worry also affected patients’ perception of cancer risk.
The authors noted that perception of risk is influenced by the individual’s personality and affect and is therefore susceptible to manipulation and distortion. Evidence from this systematic review reinforces data from a previous meta-analysis (Katapodi MC et al. 2004) in that the perceived risk of developing a heritable cancer does not correlate with the actual risk. Therefore this review is unlikely to affect future reviews of NICE CG41.

**Key reference**

**Supporting reference**


**Computer-based educational tools and decision aids**
An RCT reported by Green et al. (2004) compared the effectiveness of computer-aided decision tools with standard genetic counselling on knowledge, perceptions of risk and intentions about genetic testing for breast cancer susceptibility.

The RCT included 211 women (with personal or family history of breast cancer) recruited in 6 outpatient clinics in the USA; 105 women received genetic counselling and 106 received education by a computer program followed by genetic counselling.

The interactive and educational computer program was more effective than standard genetic counselling for increasing knowledge of breast cancer and genetic testing for women at low risk of carrying a BRCA1 or BRCA2 mutation (p = 0.03). By contrast, genetic counselling was more effective than the computer program in reducing anxiety in women at both high risk (p = 0.001) and low risk (p = 0.007), resulting in more accurate perceptions of risk. The authors concluded that the educational computer program has the potential to stand alone as an educational intervention for women at low risk, but should be used as a supplement to genetic counselling in women at high risk.

Study characteristics such as the randomisation method and comparison of the groups’ characteristics met standards for a well-designed and reported RCT. However, aspects such as drop-out analysis and blinding of the investigators were not clearly reported. The authors’ stated limitations included limited representation of the general population, lack of generalisability to other conditions, and the setting of specialist clinics.

This evidence is unlikely to affect a future update to NICE CG41 because the positive results for computer programs increasing knowledge apply only to women at low risk of mutations, who would not usually undergo genetic counselling in the UK.

Meilleur and Littleton-Kearney (2009) undertook a systematic review of 13 studies (11 RCTs and 2 ‘quasi-experimental’ studies) assessing interventions to improve patient education regarding multifactorial genetic conditions (12 studies looked at breast and ovarian cancer and 1 was of cleft lip and palate).

This review assessed the following main outcomes: objective and subjective knowledge assessment, psychological measures, satisfaction or effectiveness of intervention, time spent in counselling, decision-making, treatment choice and the value of that choice, and risk perception. Results suggested that overall, interactive computer interventions resulted in more beneficial findings, followed by video interventions. Group interventions and miscellaneous interventions did not measure all outcomes assessed in the review. The computer intervention group showed improvement in genetic knowledge, psychological
measures, satisfaction/effectiveness, time spent with counsellor, and decision/intent to undergo testing.

NICE CG41 does not mention use of interventions to help with communicating risk in people at risk of breast cancer, and this review provides limited evidence of benefit to patients, so it is unlikely to be a factor in future updates of NICE CG41.

A systematic review by Williams et al. (2008) identified and assessed interactive decision aids designed for patient or consumer use in familial breast cancer and genetic testing. One website and two CD-ROMs fulfilled all inclusion criteria; all three were developed in the USA.

When assessed against the International Patient Decision Aid Standards criteria, the decision aids did not score well, with none scoring 50% or more. The CD-ROMs were complicated to install, and sometimes required out-of-date operating systems to run. The authors concluded that although many sources of information are available, few are truly interactive or designed for use by patients.

Although the possible use of interactive decision making aids is interesting, no UK-based interventions were identified in this systematic review and the US models are likely to need modification to be suitable for the NHS. Additionally, this review did not assess clinical use of the identified decision aids, thus this evidence is not likely to impact on future updates to NICE CG41.

Key reference


1.2 Breast awareness and examination

No new key evidence was found for this section.

1.3 Care of women in primary care

Collection of family history in primary care

A systematic review by Qureshi et al. (2007) was undertaken to: evaluate the accuracy of patient reporting of cancer family history; identify and evaluate tools designed to capture genetic family history in primary care; and identify and evaluate risk assessment tools for capturing and interpreting family history.

Review of 19 eligible studies (15 case series studies and 4 case control studies; 16 assessing the accuracy of reporting family history and 3 assessing reliability; patient numbers not stated) showed reporting accuracy to be higher for relatives free of cancer (specificity; range 95–98%) than those with cancer (sensitivity; range 85–90%); better accuracy was reported for breast and colorectal cancer compared with ovarian and prostate cancer. Increased accuracy of reporting for first-degree relatives compared with second or third degree relatives was
consistently seen across studies, but other factors such as age, gender and educational level showed lesser or no clear association with accuracy of reporting.

A total of 18 family history tools applicable to primary care were identified from review of 40 eligible studies (patient numbers not stated), and mostly comprised paper-based self-administered questionnaires. Eleven tools were assessed against ‘best estimate’ genetic interviews and standard primary care practice (family history documented in medical records), the remaining seven did not assess against any comparator. Although study designs were varied, the family history tools were ‘significantly better than standard practice’.

Evaluation of 11 risk assessment tools for hereditary cancer (all included breast and ovarian cancer and some additionally included colon and prostate cancer) in computer and paper formats (patient numbers not stated) showed preliminary evidence of efficacy, although effectiveness in routine clinical practice has yet to be demonstrated.

There is a limited evidence base for the use of family history tools and risk assessment tools in primary care and extrapolation from other settings may be needed. Evidence from this systematic review is not likely to affect a future update to NICE CG41.

**Key reference**

### 1.4 Care of women in specialist (secondary and tertiary) care

#### Combined surveillance with ultrasound and mammography

A prospective, multicentre, randomised trial reported by Berg et al. (2008) assessed the diagnostic yield and performance of surveillance in 2809 women who had an elevated risk of breast cancer, comparing combined ultrasound and mammography with mammography alone.

Elevated risk was defined using a variety of criteria, including personal history, prior atypical biopsy, irradiation, Gail and Claus models, and the presence of BRCA mutations.

Ultrasound plus mammography increased cancer detection yield by 4.2 per 1000 women compared with mammography alone (95% confidence interval [CI] 1.1 to 7.2 per 1000, p = 0.003). Most cancers seen only on ultrasound were invasive, node-negative cancers. Ductal carcinoma in situ (DCIS) was better detected on mammography; five of six DCIS (83%) were only detected on mammography. However, false positives also increased with ultrasound, with false-positive rates of 4.4% for mammography alone (95% CI 3.7 to 5.3%), 8.1% for ultrasound alone (95% CI 7.1 to 9.2%); and 10.4% (95% CI 9.3 to 11.7%) for combined mammography plus ultrasound.

This study suggested that ultrasound may be better than mammography for imaging dense breast tissue and for detecting invasive breast cancers, although mammography may be better at detecting DCIS with calcifying lesions.

Combined mammography and ultrasound imaging could increase diagnostic yield and increase the sensitivity of surveillance in women with elevated risk of breast cancer. However, this could also increase the false-positive rate. Limitations of the study included lack of clarity on the design of the reference standard process.

NICE CG41 recommends that ultrasound should not be used in routine surveillance for breast cancer but may have a role in problem-solving for abnormalities detected on mammography or magnetic resonance imaging (MRI). Data from this study are unlikely to affect a future update to NICE CG41.
Magnetic resonance imaging

A systematic review of 11 prospective, non-randomised studies by Warner et al. (2008) evaluated the diagnostic accuracy of adding MRI to the annual mammographic surveillance of women at very high risk of breast cancer.

A suspicious lesion was defined as a Breast Imaging-Reporting and Data System (BI-RADS) score of 4 or 5. The summary negative likelihood ratio and the probability of a suspicious lesion were 0.70 (95% CI 0.59 to 0.82) and 1.4% (95% CI 1.2% to 1.6%) for mammography alone and 0.14 (95% CI 0.05 to 0.42) and 0.3% (95% CI 0.1% to 0.8%) for MRI plus mammography.

The authors concluded that screening with both MRI and mammography might be better than mammography alone for ruling out cancerous lesions. Of the studies included in the review, only four were not considered by the Guideline Development Group (GDG) in 2006, one of which lacked data on specificity.

Lord et al. (2007) conducted a systematic review to evaluate the effectiveness of the addition of MRI to mammography and ultrasound screening in young high-risk women.

Review of five prospective studies (2059 patients) showed that inclusion of breast MRI in conventional screening was highly sensitive (sensitivity range 93–100%) for early detection of breast cancer in young women at high risk, compared with mammography alone (sensitivity range 25–59%) or mammography plus ultrasound with or without a clinical breast exam (sensitivity range 49–67%).

Meta-analysis of the three studies of MRI plus mammography versus mammography alone showed the sensitivity of MRI plus mammography as 94% (95% CI 86 to 98%), with the incremental sensitivity of MRI at 58% (95% CI 47 to 70%). The incremental sensitivity of MRI was lower when added to mammography plus ultrasound (44%, 95% CI 27 to 61%) or to the combination of mammography, ultrasound plus a clinical breast exam (31–33%).

No studies assessed patient mortality, interval or rates of advanced breast cancer, so conclusions about the effectiveness of MRI depend on assumptions about the benefits of mammography. However, it is unclear to what extent young women at high risk receive the same benefits from early detection and treatment of MRI-detected cancers. The authors’ conclusions should be interpreted with a degree of caution because of the small number of included studies.

The systematic reviews by Warner et al. (2008) and Lord et al. (2007) discussed above reinforce NICE CG41, which recommends MRI surveillance for certain women at high risk or who have dense breasts. Only one paper included in this review (Sardanelli et al. 2007) was not considered by the GDG in developing NICE CG41; this paper also reinforces the recommendations in the guideline.

Evans et al. (2009a) undertook a post-hoc analysis of a large, multicentre UK longitudinal study, the Magnetic Resonance Imaging for Breast Screening (MARIBS) study. They reported the breast cancer incidence during the study and in extended follow-up (median follow-up in participating centres ranged from 7.1 years to 11.7 years) after MRI surveillance in 837 women at high risk.

The incidence of breast cancer was high, with 21 per 1000 developing breast cancer annually in the study and 12 per 1000 during overall extended follow-up. There was a drop-off in...
incidence after the study, despite the fact that the women were getting older and the rates would be expected to increase. The authors postulated that this was because the initial scan at study entry created a lead-time effect that was lost when the study ended.

Women whose genetic status was not known were asked to provide an anonymous blood sample at the start of the study for future mutation testing in BRCA1, BRCA2, and if appropriate, TP53. At the end of the study, the women who had developed cancer, but who had not previously had predictive genetic testing, had anonymous testing. This post-hoc analysis looked at how the results of genetic testing would have affected the study.

If genetic testing was performed before entry into the study, 171 women would have been ineligible; only one woman in this group developed breast cancer. This group had a rate of breast cancer of only 0.4 per thousand per year, which is equivalent to the risk for the average woman in the UK aged 30–39 years. The authors proposed that consideration should be given to BRCA1 and BRCA2 testing in unaffected women whose risk of having a mutation is 20% or greater (40% chance of a mutation in the family) instead of annual MRI surveillance.

In NICE CG41 annual MRI surveillance is recommended for subgroups of women at raised or high risk of breast cancer who have not undergone genetic testing, as well as for women who have tested positive for a BRCA1, BRCA2, or TP53 mutation. However, the current guidance recommends that genetic testing should begin with a family member who has had breast cancer, and if positive, genetic testing may be appropriate for unaffected family members. This means that more women would receive annual MRI surveillance than would have genetic testing. The results from Evans et al. (2009a), suggest that genetic testing could be used to determine eligibility for MRI surveillance, which may be a consideration in a future update to NICE CG41.

**Key references**

Evans DGR, Lennard F, Pointon LJ et al. (2009a) Eligibility for magnetic resonance imaging screening in the United Kingdom: effect of strict selection criteria and anonymous DNA testing on breast cancer incidence in the MARIBS study. Cancer Epidemiology, Biomarkers and Prevention 18: 2123–31. Full text: [http://cebp.aacrjournals.org/content/18/7/2123.long](http://cebp.aacrjournals.org/content/18/7/2123.long)


**Supporting reference**


**Annual mammographic surveillance for moderate risk**

A single-arm family history study (FH01) by the [FH01 collaborative teams (2010)](http://www.fh01.com) evaluated 4 years of annual mammography in women (n = 6710 women aged < 50 years; 76 centres) at moderate risk of breast cancer.

The enrolled women received annual mammography for a mean of 4 years. The FH01 study cohort was compared with two external control groups, namely, the control group of the UK Age Trial (108,971 women aged 40–42 years) and a Dutch study of women with a family history of breast cancer (aged 25–77 years). Study endpoints were size, node status, histological grade of invasive tumours and estimated mortality (based on the Nottingham prognostic index [NPI]).
A total of 136 women were diagnosed with breast cancer (105 [77%] at surveillance, 28 [21%] symptomatically in the interval between surveillance events, and three [2%] symptomatically after not attending their latest mammogram). Invasive tumours were significantly smaller (p = 0.0094) and less likely to be node positive (p = 0.0083) in the FH01 cohort than in the UK Age Trial control group, and were significantly less likely to be node positive than in the Dutch study (p = 0.012). Similarly, the mean NPI score was significantly lower in the FH01 cohort than the UK Age Trial control group (p = 0.00079) or the Dutch study (p < 0.0001). The predicted 10-year mortality was significantly lower in the FH01 cohort (1.10%) compared with the UK Age Trial (1.38%) control group (relative risk 0.80, 95% CI 0.66 to 0.96, p = 0.022).

The results suggested that 10,000 mammograms in the intermediate-risk group would prevent two deaths from breast cancer within 10 years of diagnosis, with false-positive rates similar to the NHS Breast Screening Programme. The major limitations of this study were the absence of a direct control group, and the use of predicted mortality from the NPI score (a combination of tumour size, node status, and grade).

The conclusion that yearly mammography in women with an intermediate familial risk of breast cancer is likely to be effective in prevention of deaths from breast cancer may be a consideration in a future update to NICE CG41.

Key reference
FH01 Collaborative Teams (2010) Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. Lancet Oncology. 11: 1127–34.
Abstract: www.thelancet.com/journals/lanonc/article/PIIS1470-2045(10)70263-1/abstract

Emotional distress after genetic testing

A meta-analysis of 20 prospective studies that measured emotional distress before and after genetic testing for BRCA1 or BRCA2 was conducted by Hamilton et al. (2009). Data showed that soon after receiving genetic test results, emotional distress increased slightly in people who tested positive for BRCA1 or BRCA2 mutations. However, over time distress returned to pre-testing levels.

Non-carriers and those with an inconclusive result experienced a decrease in general anxiety and cancer specific distress. However, those with an inconclusive result may misinterpret inconclusive results as an indicator of reduced risk; therefore, this group may need additional risk information. Overall, the findings indicated that BRCA1 or BRCA2 testing has minimal emotional consequences.

The authors notes that the lack of distress may be attributable to the extensive genetic counselling that participants received in the studies analysed. This reinforces the need to maintain counselling outside the controls of a trial to achieve similar outcomes.

This evidence reinforces the current perception that emotional distress associated with testing is not a substantial problem and is unlikely to affect a future update to NICE CG41.

Key reference
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC2807362/pdf/nihms162131.pdf

Genetic variation in breast cancer

A case control study from the million women initiative by Reeves et al. (2010) aimed to assess breast cancer risk in relation to 14 individual single-nucleotide polymorphisms (SNPs) previously linked to the disease, and in relation to a polygenic risk score.
Study participants were 10,306 women with breast cancer (mean age at diagnosis: 58 years) and 10,393 women without breast cancer who provided blood samples for genotyping. The authors also conducted a meta-analysis of data published in three other studies.

Key outcome measures were the estimated per-allele odds ratio (OR) for individual SNPs, and the cumulative incidence of breast cancer to age 70 years in relation to a polygenic risk score based on the 4, 7 or 10 SNPs most strongly associated with breast cancer risk.

Data from this study and the meta-analysis showed that ORs for breast cancer were greatest for FGFR2-rs2981582 and TNRC9-rs3803662 and, for these two SNPs, were significantly greater for oestrogen receptor (ER)-positive than for ER-negative disease (pooled per-allele ORs [95% CI] for ER-positive vs ER-negative disease: 1.30 [95% CI 1.26 to 1.33] vs 1.05 [95% CI 1.01 to 1.10] for FGFR2). The per-allele OR for 2q-rs13387042 was significantly greater for bilateral than unilateral disease (1.39, 95% CI 1.21 to 1.60 vs 1.15, 95% CI 1.11 to 1.20, p = 0.008) and for lobular than ductal tumours (1.35, 95% CI 1.23 to 1.49 vs 1.10, 95% CI 1.05 to 1.15, p < 0.001).

The estimated cumulative incidence of breast cancer to the age of 70 years among women in the top and bottom fifths of a polygenic risk score based on seven SNPs was 8.8% (95% CI 8.3 to 9.4%) and 4.4% (95% CI 4.2 to 4.8%) respectively; the corresponding risks for ER-positive disease were 7.4% (95% CI 6.9 to 8.0%) and 3.4% (95% CI 3.1 to 3.8%), respectively (risks for ER-negative disease were 1.4% [95% CI 1.2 to 1.6%] and 1.0% [95% CI 0.8 to 1.2%] respectively).

This study validated previously reported SNPs, but also demonstrated that the two main SNPs were more often associated with ER-positive tumours than ER-negative tumours. These data are not likely to affect a future update to NICE CG41 because this genetic research does not yet have a direct clinical application.

Key reference
Full text: www.jama.ama-assn.org/content/304/4/426.long

Risk-reducing interventions
A systematic review undertaken by Bermejo-Perez et al. (2007) comprised 18 studies (2 systematic reviews and 16 cohort or case-control studies) evaluating the effects of risk-reducing mastectomy, risk-reducing oophorectomy or salpingo-oophorectomy, tubal ligation, tamoxifen and oral contraceptive use in BRCA1 or BRCA2 carriers.

Risk-reducing mastectomy and gynaecological surgery were associated with a reduction in breast and gynaecological cancer incidence. However, the authors stated that evidence is insufficient for both chemoprevention and intensive surveillance in women with BRCA mutations. There was some evidence for a protective effect of tubal ligation on ovarian cancer, from a single case-control study.

This review reinforces the association between risk-reducing mastectomy and oophorectomy and reduced incidence of breast and ovarian cancer. This evidence is unlikely to affect any future update to NICE CG41.

A Cochrane review of ‘prophylactic mastectomy’, first undertaken in 2004, was updated (Lostumbo et al. 2010) to include 39 studies (compared with 23 in the first review). However, the conclusions did not alter as a result of the update.

All 39 reviewed studies were observational studies with some methodological limitations. In addition, older studies of bilateral risk-reducing mastectomy included women who would no
longer be considered to be at high risk and it was not possible to subdivide carriers of BRCA1 and BRCA2 mutations in the majority of studies.

The studies included data from 7384 women with a range of risk factors for breast cancer who had undergone a risk-reducing mastectomy. A total of 3657 contralateral risk-reducing mastectomy cases in breast cancer patients included in the review were outside the scope of NICE CG41; 3727 bilateral risk-reducing mastectomy cases were relevant.

The data showed reductions in incidence of breast cancer and breast cancer mortality after bilateral risk-reducing mastectomy, particularly in women at high risk of disease. Women reported satisfaction with their decisions to have bilateral risk-reducing mastectomy, but were less consistent in satisfaction with the cosmetic outcome. The majority of women reported a decreased cancer worry after bilateral risk-reducing mastectomy.

This evidence is unlikely to affect a future update to NICE CG41, which recommends raising bilateral mastectomy as a risk-reducing option with all women at high risk of breast cancer.

A long-term prospective, European multicentre study of risk-reducing mastectomy outcomes by Evans et al. (2009b) collated data from 550 women (including a high proportion of women from Manchester [total = 245, bilateral = 179]) in 10 European centres. However, 236 contralateral mastectomy cases in breast cancer patients included in the study were not relevant to NICE CG41 because this guideline did not cover treatment of breast cancer; 314 bilateral risk-reducing mastectomies were relevant. A total of 202 BRCA1 or BRCA2 mutation carriers were included in the study, however, it was not clear how many of these had bilateral surgery.

No post-surgery breast cancer had developed in women undergoing risk-reducing surgery after 2155 women-years of follow-up; a person-years at-risk analysis was used to predict the number of expected breast cancers at 21.3 cases. Accuracy of predictions of expected cancers was confirmed in a control group of at-risk women not undergoing surgery, in whom 21 cancers occurred and 20.8 were expected. In the combined bilateral and contralateral mastectomy group, 15 of 550 (2.7%) had occult malignancy at time of surgery.

This evidence reinforces recommendations in NICE CG41 and is not likely to affect a future update of this guidance.

A meta-analysis by Rebbeck et al. (2009) aimed to estimate the risk reduction for breast and ovarian cancer achieved by undertaking bilateral risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers.

Ten studies (including two case control studies and four prospective cohort studies and four retrospective cohort studies) assessed breast cancer risk reduction and ovarian cancer risk reduction. The estimated risk reduction benefits in those undergoing risk-reducing salpingo-oophorectomy compared with those not undergoing the procedure were separated for BRCA1 and BRCA2 for breast cancer, but not for ovarian and fallopian tube cancer.

A hazard ratio of 0.49 (95% CI 0.37 to 0.65) was recorded for breast cancer in BRCA1 or BRCA2 mutation carriers (three studies; 5703 patients), compared with 0.47 (95% CI 0.35 to 0.64) for breast cancer in BRCA1 mutation carriers (four studies) and 0.47 (95% CI 0.26 to 0.84) for breast cancer in BRCA2 mutation carriers (three studies; 5703 patients). An HR of 0.21 (95% CI 0.12 to 0.39) was recorded for ovarian and fallopian tube cancer in BRCA1 or BRCA2 mutation carriers (six studies; 2840 patients).

The estimates of risk reduction in this evidence may be useful to clinicians when discussing the potential benefits and risks of surgery with patients. This evidence reinforces previously published evidence and has no impact on existing recommendations in NICE CG41.
Tamoxifen for prevention of breast cancer

Tamoxifen is not currently licensed in the UK for prevention of breast cancer in people who have no history of breast cancer. However it is the subject of research to determine its potential for reducing risk of breast cancer in people at high risk.

A RCT reported by Veronesi et al. (2007) was an extended follow-up of the Italian Randomised Tamoxifen Prevention Trial among women with hysterectomy, and included subgroup analysis by risk of breast cancer.

A total of 5408 women who had undergone hysterectomy but were otherwise healthy were randomly assigned to tamoxifen (20 mg daily) or placebo for 5 years and followed-up for 11 years; 136 women (74 in the placebo group, and 62 in the tamoxifen group) developed breast cancer (risk ratio [RR] = 0.84, 95% CI 0.60 to 1.17; annual rates were 2.48 and 2.07 per 1000 women-years respectively). Rates of breast cancer in the two groups were similar among women who had had bilateral oophorectomy and among women at low risk for hormone receptor-positive (HR+) disease, but were much lower in the tamoxifen group among women at high risk (placebo, 6.26 per 1000 women-years, tamoxifen, 1.50 per 1000 women-years; RR = 0.24, 95% CI 0.10 to 0.59). These data suggest that tamoxifen may reduce the incidence of breast cancer in women who have undergone hysterectomy and are at high risk of developing hormone-related tumours.

Strengths of this study included control of bias by extensive use of appropriate statistical methods (for example, power calculations for number of participants). However, blinding of investigators and characteristics of patients who did not complete treatment were unclear. Other limitations included subgroup analysis that was not planned in the initial trial protocol.

Findings from this study represent new evidence; however, it is only applicable to women who have undergone hysterectomy. Tamoxifen is not recommended for prophylaxis of breast cancer in NICE CG41, and did not have marketing authorisation for chemoprophylaxis of breast cancer in the UK at the time of publication of this Evidence Update. This evidence is therefore not likely to affect future updates to NICE CG41.

Analysis of data from the active treatment period of the first International Breast Cancer Intervention Study (IBIS-I; Cuzick et al. 2002) showed that 5-year treatment with tamoxifen reduced the risk of invasive oestrogen receptor (ER) positive tumours by 31% in high-risk women (aged 35–70 years). A long-term follow-up analysis by Cuzick et al. (2007) presented IBIS-I data focusing on the period after active treatment.

A total of 142 breast cancers were diagnosed in 3579 women in the tamoxifen group and 195 in the 3575 women in the placebo group (4.97 versus 6.82 per 1,000 woman-years,
respectively; RR = 0.73, 95% CI 0.58 to 0.91, p = 0.004), after a median follow-up of 96 months after randomisation. The prophylactic effect of tamoxifen was generally consistent for the whole follow-up period. The benefit seemed to continue for up to 10 years after randomisation.

In addition, side effects in the tamoxifen group were much lower during the follow-up period compared with the active treatment period, for example, deep-vein thrombosis and pulmonary embolism were significantly higher in the tamoxifen group than the placebo group during active treatment (52 versus 23 cases, RR = 2.26, 95% CI 1.36 to 3.87) but not after stopping treatment (16 versus 14 cases, RR = 1.14, 95% CI 0.52 to 2.53). The risk of ER-positive invasive breast cancer was 34% lower in the tamoxifen group (87 versus 132 cases, RR = 0.66, 95% CI 0.50 to 0.87).

This study provides some evidence for tamoxifen in chemoprophylaxis of breast cancer, although tamoxifen is not recommended for prophylaxis of breast cancer in NICE CG41, and not have marketing authorisation in the UK for this indication at the time of publication of this Evidence Update. Recommendations in NICE CG41 are not likely to be affected by this evidence.

A nested case-control study within an RCT of tamoxifen versus placebo was reported by Cuzick et al (2011) and assessed whether tamoxifen-induced reductions in breast density could be used to identify women with the greatest potential to benefit from prophylactic treatment with tamoxifen.

The study included 123 women diagnosed with breast cancer at or after the first follow-up mammogram (12–18 months after study initiation) and 942 women without breast cancer (the control group). Results showed that women taking tamoxifen for 12–18 months whose mammographic density decreased by at least 10% also had a reduction in breast cancer risk (OR = 0.37, 95% CI 0.20 to 0.69, p = 0.002). However, there was no reduction in risk for women who took tamoxifen but had less than 10% decrease in mammographic density (OR = 1.13, 95% CI 0.72 to 1.77, p=0.60). By contrast, no significant difference in breast cancer risk was noted between placebo-treated women whose mammographic breast density decreased by less than 10% compared with those with greater reductions in breast density. The authors concluded that mammographic breast density measurement after 12–18 months of prophylactic tamoxifen treatment may predict response.

Limitations included lack of availability of original films and poor quality of scans. Measures were undertaken to test for and limit bias due to reader blinding and reproducibility of film judgements.

Using mammographic breast density measurement to predict response to prophylactic tamoxifen treatment needs to be confirmed in another study before adoption into clinical practice. This evidence is unlikely to affect future reviews of NICE CG41 because tamoxifen is not licensed for prevention of breast cancer in the UK.

Key references


Supporting reference

Uptake of breast cancer chemoprevention
A systematic review by Ropka et al. (2010) evaluated the uptake of chemoprevention with tamoxifen or raloxifene by women at high risk of breast cancer. Thirteen studies (n=10,383) were identified (four looked at real chemoprevention decisions, eight examined hypothetical decisions and one study investigated both). No RCTs, cohort studies or case-control studies were identified; all 13 studies were of correlational or descriptive study design.

The nine studies (n = 10,023) addressing hypothetical uptake found a mean uptake rate of 24.7% (range 5.7–60.0%), although this may not accurately reflect actual uptake. The five studies (n = 992) about real, as opposed to theoretical, uptake found a mean uptake of 14.8%, but with substantial variation between studies (range 0.5–51.2%). Perceived risk of breast cancer was associated with increased uptake and concern regarding side effects was associated with reduced uptake. This review did not include any studies from the UK.

Some of the studies included in this systematic review had methodological flaws that may have influenced and biased chemoprevention uptake rates, for example, less than 50% of the studies used a sampling strategy that could permit reliable reproduction of the study groups and none were RCTs.

Neither tamoxifen nor raloxifene are recommended in NICE CG41 for prevention of breast cancer and did not have marketing authorisation for this indication in the UK at the time of publication of this Evidence Update. This evidence therefore has no impact on NICE CG41. A study has also shown that uptake of chemoprevention trials is low and greater recruitment to such trials is needed to evaluate whether chemoprevention is effective (Evans et al. 2010).

Key reference

Supporting reference

1.5 Risk factors
A meta-analysis of 34 case control studies was undertaken by Kahlenborn et al. (2006) to determine whether previous use of oral contraceptives is associated with premenopausal breast cancer.

The authors concluded that use of oral contraceptives was associated with an increased risk of premenopausal breast cancer (OR = 1.19, 95% CI 1.09 to 1.29). Furthermore, use of oral contraceptives was associated with breast cancer risk in both parous (OR = 1.29, 95% CI 1.20 to 1.40) and nulliparous women (OR = 1.24, 95% CI 0.92 to 1.67). Although a longer period of oral contraceptive use did not significantly impact breast cancer risk in nulliparous (OR = 1.29, 95% CI 0.85 to 1.96) women, the risk was increased when oral contraceptives were used before (OR = 1.44, 95% CI 1.28 to 1.62) the first full-term pregnancy than after
(OR = 1.15, 95% CI 1.06 to 1.26) in parous women. Breast cancer risk was most increased for parous women with 4 years use of oral contraceptives or longer before the first full-term pregnancy (OR = 1.52, 95% CI 1.26 to 1.82).

Limitations of the review include a lack of assessment of the scientific quality of the included studies or details on the assessment of publication bias. Self-reported limitations included the need for more data on individual participants and controls, lack of prospective studies, and inability to adjust for confounders such as hormonal doses.

Gaffield et al. (2009) conducted a systematic review including one meta-analysis and ten other studies (seven case-control studies, two cohort studies, and one unspecified design), including more than 200,000 women, to examine whether the use of combined oral contraceptives changes the risk of developing breast cancer in women of reproductive age with a family history of breast cancer.

The narrative review found that seven of the included studies and the one pooled analysis (three of which were deemed good quality, two fair and three poor by the authors) indicated that women are not at greater risk of breast cancer after oral contraceptive use. By contrast, the remaining three studies (two of which were deemed to be of fair quality and one poor by the authors; over 14,000 women included in total) indicated that use of oral contraceptives was significantly associated with risk of breast cancer in women with a familial history of breast cancer, particularly if they used oral contraceptives before 1975.

The review had a number of limitations, for example no information was provided regarding study design, inclusion criteria, quality assurance of searching, sifting or data extraction, tests for heterogeneity, or assessment of publication bias. Furthermore, there was a wide variation in the description of patients’ medical history. However, it included detailed reporting of the characteristics of included studies, and grading of the included studies using the US Preventive Services Task Force grading system.

Although the evidence from Gaffield et al. (2009) contradicts that reported above by Kahlenborn et al. (2006), both reviews highlight the prevailing uncertainties regarding the relationship between use of oral contraceptives and familial breast cancer. The evidence does not affect current recommendations about hormonal contraceptives in NICE CG41.

Key references

Full text: www.mayoclinicproceedings.org/article/S0025-6196(11)61152-X/fulltext
2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Approaches to care for all women

- Cancer genetic risk assessment for individuals at risk of familial breast cancer
  [Link](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411907)

Care of women in specialist (secondary and tertiary) care

- Contralateral prophylactic mastectomy for women with breast cancer
  [Link](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=412300)


DUETs has been established in the UK to publish uncertainties about the effects of treatment which cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.
Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:


Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the period from 1 March 2002 (the beginning of the searches for the NICE clinical guideline 41) to 10 August 2011:

- Cochrane (CDSR, CENTRAL/CCTR, DARE)
- CINAHL
- EMBASE
- Medline (including Pre-Medline and In-Process citations)
- PsycInfo

The search strategy for this Evidence Update was based on the scope and search strategy from NICE CG41. Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

Eight other studies (Berg et al. 2008, Cuzick et al. 2007, Evans et al. 2009a, Evans et al. 2009b, FH01 Collaborative Teams 2010, Gaffield et al. 2009, Rebbeck et al. 2009, Reeves et al. 2010) were also identified outside of the literature search. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies, are available on request from contactus@evidence.nhs.uk
Table 1 MEDLINE search strategy (adapted for individual databases)

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<th>exp Genetic Testing/</th>
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**Figure 1 Flow chart of the evidence selection process**

2855 records identified through search

1688 records after duplicates removed

514 records included after first sift

136 records included after second sift

43 records included after review

42 records included after critical appraisal

23 records included by EUAG in published update

1167 duplicates from searching

1174 records excluded after first sift

378 records excluded after second sift

101 records excluded after review by Update Adviser. 8 additional records identified by EUAG.

1 record excluded after critical appraisal

19 records excluded by EUAG

EUAG – Evidence Update Advisory Group
Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

Dr Chris Alcock – Chair
Consultant Clinical Oncologist, Oxford Radcliffe Hospitals NHS Trust and Clinical Lead, NHS Evidence

Mr Andrew Baildam
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