NICE National Institute for Health and Care Excellence

# 2019 exceptional surveillance of familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (NICE guideline CG164)

Surveillance report

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# Contents

# Surveillance decision

We will not update the guideline on familial breast cancer.

We will refresh recommendation 1.6.5 to clarify the decision-making process that is involved in considering whether women aged 30 to 39 at high risk of breast cancer have annual mammographic surveillance.

# Reasons for the decision

## Assessing the evidence

The purpose of this exceptional review was to examine any impact of the findings of a cohort screening study, Final results of the prospective FH02 mammographic surveillance study of women aged 35–39 at increased familial risk of breast cancer (Evans et al. 2019), on the NICE guideline on familial breast cancer (CG164).

Because of concerns about the link between radiation exposure from mammography and breast cancer, we also considered a Public Health England (PHE) report on radiation risk with digital mammography in breast screening (PHE 2017). No additional evidence published since the end of the search period for the 2018 surveillance review (13 June 2017) was considered by the exceptional review.

## Study summary

### Methods

The study reports on the findings of a UK prospective cohort study (FH02) that assessed whether annual mammography screening in women aged 35 to 39 years who have a family history of breast cancer or genetic predisposition for breast cancer is effective at detecting breast cancer at an early stage. Women were recruited from December 2006 to December 2015 in 34 UK centres (n=2,899), with data from 2,820 women available. Women were also followed up until December 2016 (to ensure at least 12 months' follow-up from screening) and cancer registration was checked in December 2017. There were 12,086 annual screening mammograms over the study period.

Eligibility criteria for the trial were based on having a family history of breast cancer or being a BRCA1 or BRCA2 mutation carrier or having at least a 1 in 4 risk of carrying a known mutation in a family. Women were categorised using the Tyrer–Cuzick algorithm as high risk (8% or more 10-year risk with age set at 40 years regardless of age at entry; n=344), moderate risk (3% to 7.99% 10-year risk; n=1,977) or 'near average risk' (less than 3% 10-year risk; n=499). These criteria are the same as those used in the recommendations in NICE guideline CG164 to determine high, moderate and 'near population' risk in women aged between 40 and 50 years.

Exclusion criteria included: women aged below 35 and above 39 years at time of recruitment, pregnancy, 'a previous history of breast cancer or ductal carcinoma in situ or bilateral risk-reducing mastectomy', contraindication to annual X-rays, cancer detected by MRI rather than mammography.

The recorded outcome measures for all participants enabled the calculation of breast cancer incidence, diagnostic accuracy of mammographic surveillance, radiation dose from mammography where available (mean glandular dose [MGD] per image); and clinical and pathological data were collected for each cancer diagnosed at a screening episode or as an interval cancer (cancer diagnosed in between routine screening episodes).

Screening accuracy of annual mammography in the FH02 prospective cohort was compared with those of the FH01 prospective cohort screening study (Duffy et al. 2010) and the UK age randomised controlled trial (Moss et al. 2006), which both assessed the effectiveness of annual mammography in women aged 40 to 49 years. Clinical and pathological data in FH02 prospective study (tumour size and lymph node status) were compared with the findings reported in the 'germline BRCA mutation and outcome in young-onset breast cancer' (POSH) prospective cohort study, which recruited women with incident breast cancers aged 40 years or younger in the UK from 2000 to 2007 (Copson et al. 2018) in order to compare prognostic indicators for breast cancer between these cohorts.

## Results

### Breast cancer incidence

Overall, a total of 55 breast cancers in 54 women occurred during the whole study period (1 bilateral), with 50 cancers in 49 women (15 carcinoma in situ) adherent to the screening, with 37 of the cancers detected at mammography screening. This gave an overall

incidence of 3.9 per 1,000 when followed up to a maximum age of 49 years and excluding prevalent screen detected cancers (those diagnosed in the first screening round; n=3).

When followed up to and including those aged 41 years, incidence rates were 10.3 per 1,000 in the high-risk group (95% confidence interval [CI] 5.7 to 18.6), which is within the NICE threshold for 10-year risk for this population but does also cross the boundary for 'moderate risk'. In the FH02 moderate risk group, incidence was 2.7 per 1,000 (95% CI 1.6 to 4.4) and 1.2 (95% CI 0.2 to 4.9) in the average risk group, indicating no significance difference in incidence of breast cancer between these groups and an incidence that does not differ significantly from the NICE threshold for 'near population' risk.

**Diagnostic accuracy**

Programme sensitivity was calculated as 72% (95% CI 59% to 85%), mean sojourn time (the duration of the time period between a cancer being screen detectable and the time that the cancer shows symptoms or is clinically diagnosed) was estimated as 1.8 years and test sensitivity as 93% (95% CI 0.68 to 0.99), which was higher than the programme sensitivity because sojourn time was taken into account. The sensitivity of the screening programme in FH01 was 79%. Although the authors reported that 'to have 90% power [to] detect a significant S [programme sensitivity] ... we would need 65 cancers screen detected plus interval cancers (those presenting symptomatically within 1 year) in total' (that is, there were fewer cancers than needed to detect programme sensitivity), the estimation of the sample size may have been overly conservative, and the confidence interval range indicates that the result should be considered as significant at the 5% level.

Overall, 6% (729/12,086) of mammograms led to a recall of patients. There were 191 breast biopsies, resulting in 37 screen-detected cancers. There were '20 recalls per cancer screen-detected, 19 false positives per screen-detected cancer, and 5 biopsies per cancer screen-detected'.

**Clinical outcomes**

Eighty percent (28/35) of invasive cancers were 2 cm or less and 80% were also lymph node negative; these invasive cancers were significantly smaller and significantly less likely to be lymph node positive than invasive cancers in the comparison POSH study cohort.

There were no results on survival and mortality. Ten-year survival was projected based on

tumour attributes at diagnosis, which was calculated as 79%. This was compared with (an estimated) 71% 10-year survival in the POSH study, leading to an estimated relative mortality of 0.72 (95% CI 0.49 to 1.07). The study authors state that the reason there is no significant difference between the study findings for survival is that 'the study was not powered for this analysis'. The study authors plan further work to follow up on actual mortality in the future.

**Radiation exposure**

For women aged 35 to 39 years, the MGD per 'standard sized breast' was 1.5 mGy (that is, 3 mGy for a two-view examination).

**Genetic testing**

Systematic genetic testing was only undertaken in 1 of the 34 participating centres. In that centre, there were 22 breast cancers, with 6 having a pathogenic BRCA1 (4 of whom had been undergoing concurrent MRI) and 4 having a BRCA2 variant (11 had no pathogenic variant identified and 1 was untested). Twenty-three centres submitted BRCA data for 1,593 women, with 28 (1.76%) identified as being pathogenic variant carriers.

## Previous surveillance

There have been 2 previous surveillance reviews of NICE guideline CG164.

The surveillance review in November 2015 found no evidence relevant to recommendations on mammographic surveillance of women aged under 40 years with a family history of breast cancer.

In the January 2018 surveillance review, 2 relevant studies were identified. One study (Phi et al. 2016) looked at the additional contribution of mammography to screening accuracy in BRCA mutation carriers of all ages screened with MRI (n=1,951). This reported that in BRCA1 and BRCA2 mutation carriers of all ages, the addition of mammography to MRI did not significantly increase screening sensitivity. However, in women with BRCA2 mutation younger than 40 years, one-third of breast cancers were detected by mammography only. The authors report that 'proper repair of DNA double-strand breaks that are caused by low-dose X-rays is impaired at any age in both BRCA1 and BRCA2 mutations carriers … This makes BRCA1 and BRCA2 mutation carriers more susceptible than non-carriers, possibly also at older ages, to the cumulative effect of yearly mammograms. Given these

potential disadvantages of mammography, it is important to balance the potential benefits and harms of mammography screening in BRCA1/2 mutation carriers. Hence, substantial early detection of breast cancer by mammography is needed to outweigh the potential harm of cancer induction'.

Another comparative study (Riedl et al. 2015) evaluated the breast cancer screening efficacy of mammography, ultrasound and MRI in high-risk women with either a BRCA mutation or a high familial risk, categorised as having a greater than 20% lifetime risk (n=559 women aged 22 to 83 years, with a median age of 44 years). This reported that the sensitivity of MRI (which was 90.0%, 95% CI 76.9% to 96.0%) was significantly higher than that of mammography (37.5%; 95% CI 24.2% to 53.0%) or ultrasound (37.5%; 95% CI 24.2% to 53.0%). Age, mutation status, and breast density had no influence on the sensitivity of MRI and did not affect the superiority of MRI over mammography or ultrasound.

It was concluded that the findings of these studies did not have an impact on the recommendations in NICE guideline CG164 because overall, the studies' findings support the recommendations to consider annual mammographic surveillance and offer annual MRI surveillance to certain 'high-risk' women (see the section on recommendations below).

## NICE guideline CG164

### Recommendations

NICE guideline CG164 includes recommendations on mammographic surveillance for women with a family history, but no personal history of breast cancer, by age group and risk profile for developing breast cancer (recommendations 1.6.3 to 1.6.6):

- It is recommended that women aged 40 years or over with a moderate or high risk of cancer are offered annual mammographic surveillance (**recommendation 1.6.3**); and that annual mammographic surveillance is 'considered' for women aged 30 to 39 years meeting the following criteria:
  - high risk of breast cancer but with a 30% or lower probability of being a BRCA or TP53 carrier
  - not had genetic testing but have a greater than 30% probability of being a BRCA carrier
  - known BRCA1 or BRCA2 mutation (**recommendation 1.6.5**)

The guideline also recommends that women aged 30 to 39 years at moderate risk of breast cancer are not offered mammographic surveillance (**recommendation 1.6.6**).

It should also be noted that there are recommendations on MRI surveillance for women with no personal history of breast cancer, which recommend offering annual MRI surveillance to women aged 30 to 49 years who have a known BRCA1 or BRCA2 mutation or who have not had genetic testing but have a greater than 30% probability of being a BRCA carrier (**recommendation 1.6.7**).

It is recommended that MRI is not offered to women 'of any age at moderate of breast cancer' or 'at high risk of breast cancer but with a 30% or lower probability of being a BRCA or TP53 carrier' (**recommendation 1.6.9**).

## Guideline development

In the development of NICE guideline CG164, studies were identified that addressed the review question: 'What are the specific surveillance needs of women with a family history who have no personal history of breast cancer?'

### Diagnostic accuracy

Moderate quality evidence from 14 studies assessing the diagnostic accuracy of screening in women at high risk of familial breast cancer or with a proven mutation suggested that 'surveillance using MRI has better sensitivity for breast cancer than mammography, clinical breast examination or ultrasound. Surveillance with both MRI and mammography has better sensitivity than either test alone' (NICE full guideline CG164, 2013). Both mammography and MRI had high levels of specificity but mammography had a significantly

higher specificity than MRI, there were no significant differences between the tests for positive predictive value, but MRI had a significantly lower negative predictive value than MRI. All but 1 study included women aged 35 to 39 years. Of note, in 1 study the relative sensitivity of mammography and MRI surveillance in different age groups was assessed and it was found that MRI had better sensitivity than mammography in women younger than 40 years (61% versus 33% respectively), aged 40 to 49 years (83% versus 39%) and at 50 years or older (67% versus 56%).

**Clinical outcomes**

One systematic review of case-control studies and 3 observational studies (including the FH01 study) were identified that addressed the clinical efficacy of surveillance in women at high risk of familial breast cancer. The studies all assessed annual mammography screening, but not MRI screening. The observational studies included women aged 50 years or younger: this included the FH01 study which only included women aged 40 to 50 years, whereas the other 2 studies included women aged 35 to 50 years. Clinical outcomes in the intervention arm of the observational studies were all compared with a comparison cohort.

The evidence (assessed as very low quality) indicated that invasive breast cancers diagnosed in mammography-screened women aged 50 years or less with a family history of breast cancer, are significantly smaller and significantly less likely to have positive nodes at diagnosis than those diagnosed in unscreened women of a similar age. A disease-specific survival benefit with mammographic surveillance in women aged less than 50 years with a family history of breast cancer was also found.

**Incidence of radiation-induced cancer**

Low-quality evidence from a systematic review indicated that exposure to low-dose radiation during screening mammography or chest X-ray is associated with a non-significant increased risk of breast cancer in women with a familial or genetic predisposition. But there was evidence of a dose-response relationship between low-dose radiation and breast cancer in this population, with exposure before the age of 20 years or to 5 or more exposures significantly increasing the risk of breast cancer.

**Health economic considerations**

A cost-effectiveness review identified 5 papers that reported on the cost-effectiveness of

different screening strategies compared with no screening or each other. Four studies were conducted in the US and 1 was based in a UK healthcare setting. The papers reported varying degrees of cost effectiveness, but results were inconsistent for the different screening strategies.

A health economic model (Markov model) was developed to assess the cost effectiveness of no screening, annual mammography, annual MRI scans and a combination of annual mammography and MRI scans in women with a family history who have no personal history of breast cancer, for different age groups and for different levels of breast cancer risk. The model used data on film-screen mammography only, used a sensitivity figure of 40% for mammography (which was adjusted for age: under 30% sensitivity in women aged 30 years, up to a maximum of just under 50% in the 55 to 65 years age range), and for radiation dose, assumed that each woman received a mean glandular radiation dose of 4.5 mGy for each two-view mammography screening. It should be noted that digital mammography is now routinely used in the NHS, the potential implications of which are discussed in the impact section.

The results of the model indicated that in the high-risk group, for women aged 30 to 39 years, there is supportive evidence for the use of annual mammography or using MRI screening as an alternative to mammography, with evidence against the use of combining this with annual MRI. It was reported that in the 'raised risk' group aged 30 to 39 years, 'there is no evidence supporting cost effectiveness of annual screening'.

Because of concerns about the uncertainty surrounding the effect of radiation on developing breast cancer and given its cumulative effect, the group 'were unwilling to recommend routine annual mammography in this age group'. The model was therefore also run with MRI and 'no screening' as the only options for this age group. It was reported that MRI is cost effective in BRCA1 mutation carrier population, is 'uncertain' in the high-risk group, and is not cost effective for the 'raised risk individuals' relative to no screening.

## Views of topic experts

In this exceptional review, we engaged with topic experts who were members of the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We received responses from 3 topic experts, all of whom felt the guideline should be updated. The topic experts included a professor of medical genetics and cancer epidemiology, a research genetic counsellor, and programme manager for PHE's breast screening programme. One of the topic experts was involved in the FH02 study.

All the topic experts responded that the study's findings on the incidence of breast cancer and clinical outcomes indicate that recommendation 1.6.5 on considering annual mammographic surveillance for women aged 30 to 39 years should be changed from 'consider' to 'offer' in women at high risk of breast cancer aged 35 to 39 years (that is, a change to the strength of the wording of the recommendation). Two experts highlighted that in practice, women in this age group who are at high risk of breast cancer are infrequently offered annual mammographic surveillance in England, one of whom indicated that this was because of the wording of the recommendation is to 'consider' rather than 'offer' mammographic surveillance.

Views concerning whether women aged 35 to 39 years at moderate risk of breast cancer could or should be offered annual mammographic surveillance varied. Topic experts noted that this may require health economic assessment; one expert noted that although the incidence rate of breast cancer in the FH02 study was below the expected rate for a moderate risk population, they felt that screening may be justifiable in terms of life expectancy gains, but noted that the relative benefit of an additional 5 mammography exposures for moderate risk cases would be less in this population than in women at high risk. They noted the importance of providing high-quality information concerning the benefits and risks associated with additional radiation exposure when offering screening. All topic experts thought that the benefits of early diagnosis in women at high risk aged 35 to 39 years were likely to outweigh the potential harms from increased radiation exposure.

## Equalities

The study under review highlighted a potential issue with equity to access to care for sisters with different reproductive risk factors because they may gain entry to screening at different ages. This however would be the case for all screening that has specific entry criteria.

## Impact

NICE guideline CG164 currently recommends considering annual mammographic surveillance to women within the age group of 35 to 39 years who are at high risk of familial breast cancer and have no personal history of breast cancer and to offer annual MRI surveillance to certain groups of high-risk women. Neither annual mammographic nor MRI surveillance is recommended for women aged 35 to 39 years at moderate risk of familial breast cancer.

The FH02 study reported that the incidence rates of breast cancer were 10.3 per 1,000 in the high-risk group when followed up to 41 years and that if cancer is detected early in women aged 35 to 39 years who are at risk of familial breast cancer, they have better clinical outcomes (smaller tumours that are less likely to be lymph node positive). This highlights the importance of considering providing annual mammography to high-risk women, but because of ongoing concerns about the impact of radiation exposure from mammography, and the available option of MRI for some of this population, it is not deemed appropriate at this point to consider that all high-risk women are offered mammographic surveillance. It should also be noted that there are several limitations to the FH02 study, including the inherent limitations associated with the observational study design (more prone to bias and confounding than experimental studies), a lack of results on survival and mortality, and limitations in the reporting of population characteristics and data, which are discussed below.

Data and analyses were not reported consistently in terms of whether the individual was at high risk because of a family member with a history of breast and/or ovarian cancer, a BRCA1 or BRCA2 mutation, or because of a 1 in 4 risk of carrying a known mutation in a family. NICE guideline CG164 carefully considered the surveillance needs of the different subgroups of high-risk women. The finding in the FH02 study that over 40% of women diagnosed with breast cancer in 1 centre were BRCA1 or BRCA2 mutation carriers is of importance because NICE guideline CG164 already recommends that these women are offered annual MRI screening (recommendation 1.6.7) and, as with all high-risk women, that mammography is considered (recommendation 1.6.5). As noted, there are concerns about the impact of radiation exposure on women at high risk of breast cancer, especially in those who are BRCA1 or BRCA2 mutation carriers, and so it is considered prudent that careful consideration is given as to whether mammography is appropriate for this population or not. The need to provide information to patients on the risks and benefits of mammography, including 'the risk associated with exposure to radiation' are highlighted in recommendation 1.6.18. It is however of concern that topic experts have reported that in practice, women aged 35 to 39 years who are at high risk are not being considered for mammography. It is therefore deemed important that further work is undertaken to ensure that recommendation 1.6.5 is being interpreted as intended. As a first measure, we have added the following wording to recommendation 1.6.5: 'Discuss the benefits and risks of mammographic surveillance with the person before making a shared decision on how to proceed, as described in recommendation 1.6.18.'

With regard to the risks of breast cancer from radiation exposure, it is acknowledged that the health economic modelling work that informed the recommendation decisions in NICE

guideline CG164 was based on data on film-screen mammography rather than digital mammography, which may have underestimated the sensitivity of mammography in detecting breast cancer in younger women and used a radiation dose that is 50% higher than the currently accepted radiation dose from digital mammography (4.5 mGy for film-screen rather than 3.0 mGy for each two-view digital mammography screening; PHE 2017). The PHE report also provides information on the number of radiation-induced cancers in England, but the figures are for the general population and not for women under 47 years. The population of interest here are younger women at high risk of breast cancer who have been described as at greater risk of developing cancer due to radiation exposure (especially in BRCA1 and BRCA2 mutation carriers). Further work to clarify the risks of radiation exposure from digital mammography in women younger than 40 years at risk of familial breast cancer is required before this area is considered for update.

Within guideline development, for a committee to recommend that something is 'offered', 1 of the criteria is that the benefits of the intervention must 'clearly outweigh the harms for most people' (see the section on writing the guideline in developing NICE guidelines: the manual). It is our conclusion that, given the concerns about radiation-induced breast cancer and the uncertainty about the risks of radiation-induced cancer in this population, it is unlikely that a committee could meet the requirements stated in the NICE guideline manual for changing recommendation 1.6.5 from 'consider' to 'offer' annual mammographic surveillance to women aged 30 to 39 years at high risk of breast cancer.

In relation to suggestions that NICE guideline CG164 should be updated to recommend that women aged 30 to 39 years at moderate risk of breast cancer are considered for mammographic surveillance, there was no significant difference in the incidence of breast cancer between the 'moderate risk' and 'average risk' groups. Coupled with the findings in guideline development that mammographic surveillance is not cost effective in this population, there is no clear rationale to recommend an update of recommendation 1.6.6, which recommends that women aged 30 to 39 years at moderate risk of breast cancer are not offered mammographic surveillance.

# Overall decision

After considering the impact on current recommendations of the evidence, topic experts views and other intelligence, we have decided not to update NICE guideline CG164 at this time. Recommendation 1.6.5 has been refreshed to improve the implementation of this recommendation.

# How we made the decision

Exceptionally, significant new evidence may mean an update of a guideline is agreed before the next scheduled check of the need for an update. The evidence might be a single piece of evidence, an accumulation of evidence or other published NICE guidance.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

## Evidence

This surveillance report provides an overview of a cohort screening study published since the publication of NICE guideline CG164. The results of this study, alongside topic expert feedback, were considered in detail to determine if there was an impact on the recommendations within NICE guideline CG164.

## Views of stakeholders

Because this was an exceptional surveillance review, we did not consult on the decision.

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