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Report of the Working Party for Higher Risk Breast Screening

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Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Prepared by: Professor Lars Holmberg
Editor Dr Kiera Chapman, NHS Cancer Screening Programmes

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Contributors

Professor Lars Holmberg (Chair)
Professor of Cancer Epidemiology,
Division of Cancer Studies, King's College London School of Medicine

Professor Ian Ellis
Professor of Cancer Pathology,
Molecular Medical Sciences Department, Histopathology, City Hospital Nottingham

Dr Louise Izatt
Consultant in Cancer and Clinical Genetics,
Clinical Genetics Department, Guy's Hospital, London

Dr Michael Michell
Consultant Radiologist,
Breast Radiology Department, King's College Hospital, Denmark Hill, London

Dr Caitlin Palframan
Policy Manager: Genetics,
Breakthrough Breast Cancer, Weston House, 246 High Holborn, London

Dr Gillian Reeves
Statistical Epidemiologist, Cancer Epidemiology Unit, University of Oxford, Richard Doll Building, Roosevelt Drive, Oxford

Dr Robin Wilson
Consultant Radiologist,
The Royal Marsden NHS Foundation Trust, Breast Unit, Fulham Road, London

Professor Ken Young
Consultant Physicist, National Coordinating Centre for the Physics of Mammography, Medical Physics Department, Royal Surrey County Hospital, Guildford

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The working party acknowledges essential input from Prof Sarah Pinder for section 2.4, excellent administrative support from Mrs Rosemary Drescher, and funding from the Department of Health.

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Executive summary

In January 2009, Professor Julietta Patnick (Director of NHS Cancer Screening Programmes) and Professor Valerie Beral (Chair of the Advisory Committee for Breast Cancer Screening) appointed a working party to develop practical recommendations for the surveillance of women at high risk of developing breast cancer. The recommendations were to be based on NICE guidelines and developments in the screening programme.

The working party has considered:

- the level of risk of breast cancer
- the risk of dying from breast cancer
- the risks posed by the radiation associated with mammographic screening
- the size of the populations that are subject to certain risk factors

The working party has not considered or reviewed:

- all the underlying scientific evidence defining each risk factor
- the evidence for the quality of a specific marker or test for risk
- the growth rate of tumours given a defined set of risk factors
- the detectability by mammography of cancers with different aetiologies
- the curability of breast cancer, given that the tumours are detected at different stages, according to their aetiology

The working party's conclusions are based on models investigating the effect of changes to the screening programme, epidemiological data on patterns of risk in women with high hereditary risk, the health technology assessment (HTA) outline recommendations for the surveillance of women with a previous breast cancer, and a commissioned report on epidemiological risk factors. The relationship between histopathological findings of premalignant states in the breast and breast cancer risk was also considered. The working party based their discussions on a range of programmes that were assumed to be logistically manageable, which were derived from current screening suggestions for women with a higher risk of breast cancer.

The primary measure of effectiveness was the net change in breast cancer mortality associated with each screening programme, as compared to standard screening. The results from the models are presented alongside the number of women who need to be screened (n=278), and the overall number of screens

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required (n=2000) in the routine NHS breast screening programme (NHSBSP) to prevent 1 breast cancer death in the screened population.

At a level of relative risk (RR) of 3 to 4 compared to the average population, a more intense screening programme starts to have benefits for high-risk women, reducing the number of deaths per number of women screened, or per the number of screens regarded as acceptable within the existing NHSBSP. For women with a very high risk (a RR of around 8 or greater compared to the general population), a more intense programme has substantial beneficial effects.

Women with a RR of 3 or greater do not constitute more than 6% of the population in any age group between 40 and 75 years. It should be noted that the majority of breast cancers in the population derive from women considered to be at low or average risk.

The working party therefore recommends an extended programme of mammography for women at a RR of 3 to 7 compared to the general population. A programme combining MRI and mammography is recommended for women with a RR of 8 or greater.

Identifying women at high risk of breast cancer poses problems. It is relatively straightforward to identify individuals who have undergone consultation at family genetics clinics, who have received treatment with supradiaphragmatic irradiation (SDI) at a young age, or who have undergone an operation for a premalignant breast condition, however, there is currently no mechanism in place to identify women with combinations of epidemiological risk factors that lead to an individual RR of 3 or greater compared to the general population. If a more intense screening protocol for all women with an RR of 3 or greater is considered a priority, such a mechanism will have to be put in place. Additionally, there is a need to consider how mammographic surveillance of women with a previous breast cancer can best be standardised.

The working party acknowledges that there are three major difficulties in providing evidence to underpin the recommendations in this report. First, there is little randomised data available for many of the underlying determinants of an effective screening programme; second, the modelling of the benefits that would be achieved by different programmes is sensitive to assumptions; and third, programmes would ideally be based on substantially more knowledge about their performance in relation to tumour biology. Therefore, when new evidence of relevance to these recommendations emerges, the recommendations should be reviewed.

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The working party also recommends that the different initiatives and projects that are currently considering the surveillance of women at high risk of breast cancer should be aligned.

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1.Introduction

1.1. Remit

In January 2009, Professor Julietta Patnick (director of the NHS cancer screening programmes) and Professor Valerie Beral (chair of the Advisory Committee for Breast Cancer Screening) appointed a working party to recommend protocols for screening women at high risk of breast cancer. The working party formed part of the Advisory Committee for Breast Cancer Screening, which operates independently of the national breast screening programme.

The objective of the working party was summarised as follows:

> To develop practical recommendations, based on NICE guidance and subsequent developments in the screening programme, for the surveillance of women at high risk of developing breast cancer. The recommendations should benefit these women without compromising the existing, high-quality, population-based screening programme. In addition, the working party should consider the policies covering the surveillance of women with a previous diagnosis of early and locally advanced breast cancer, to ensure that their management is stratified in line with their risk.

The Advisory Committee agreed that those centres already organising screening for women identified as high-risk by family genetics clinics should not suspend their activities while awaiting the results of the working party and the final decision of the Advisory Screening Committee.

1.2. Background

The establishment of a working party stemmed from discussions at the Advisory Committee about the screening policy for women at a moderately high risk of breast cancer. While there is general agreement on the need for a small group of women at very high risk to undergo more intensive screening, the question of whether women at moderately high risk should be offered a more intensive programme remains a subject of debate.

First, an inclusive definition of ‘moderate risk’ could identify a very large number of women as candidates for screening, potentially threatening the logistics of the routine mammography screening programme. Second, while some women at

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moderately high risk can be readily identified (eg by family history, genetic testing, or presence of a specific biomarker), women with a number of epidemiological risk factors that combine to form an equivalent moderate level of risk are often more difficult to identify. Ensuring that the latter group have equal opportunities for diagnosis and treatment within the programme remains a challenge. Third, in practical terms, it is important that the routine screening programme is not burdened with a large number of complicated protocols (it was originally envisaged that there should be 3 or 4 generic protocols in total).

It was acknowledged that it would be impossible for the working party to review all the evidence required to characterise all of the different risk subsets of women. Rather, the working party was asked to find a generic solution, and to develop a scheme to allow new proposals for markers of high risk, and their consequences for screening policy, to be discussed and determined.

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1.3. Scope and limitations

The working party has considered:

- the level of risk of breast cancer
- the risk of dying from breast cancer
- the risks posed by the radiation associated with mammographic screening
- the size of the populations that are subject to certain risk factors
- age at onset of risk

The working party has not considered or reviewed:

- all the underlying scientific evidence defining each risk factor
- the evidence for the quality of a specific marker or test for risk
- the growth rate of tumours given a defined set of risk factors
- the detectability by mammography of cancers with different aetiologies
- the curability of breast cancer, given that the tumours are detected at different stages, according to their aetiology

Ideally, several of these factors would be considered when providing a strong recommendation concerning screening interval and the age range for invitation, however, our current knowledge of the association between any given risk factor and the natural history of breast cancer is very limited. In the absence of data from randomized trials, estimates of screening's effectiveness under different scenarios (varied by method, age group, and interval) had to be based on indirect evidence.

The working party has not estimated the cost of different programmes.

1.4. Approach

The working party based their discussions on a range of programmes derived from current screening suggestions for women with a higher risk. All of the programmes considered were assumed to be logistically manageable.

The working party based their conclusions on:

- models developed by Dr Gillian Reeves' group in Oxford, which assess the effects of changes to the screening programme[1]
- epidemiological data from Dr Izatt on patterns of risk in women with high levels of hereditary risk
- the health technology assessement (HTA) recommendations for the surveillance of women with a previous breast cancer,[2] generously provided to the group prior to publication by professor Fiona Gilbert
- a commissioned report on epidemiological risk factors, compiled by professor Max Parkin, Dr Maribel Almonte, Dr David Mesher, and professor Peter Sasieni[3]

The relationship between histopathological findings of premalignant states in the breast and breast cancer risk was considered via consultation with professor Ian Ellis and professor Sarah Pinder.

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2.Findings

2.1. Estimating the net effect on breast cancer mortality of possible screening interventions aimed at women with greater than average risk

2.1.1. Programmes considered

The working party considered the likely effect on breast cancer mortality of a number of possible breast cancer screening protocols aimed at women with a greater than average lifetime risk of developing the disease.

The proposed screening protocols fall into 2 categories: those aimed at women who are at very high risk of the disease because they are carriers of a high-penetrance mutation; and those aimed at women who do not have a strong hereditary risk, but who have a substantially greater than average lifetime risk.

For women with a very strong hereditary risk, the group considered the effect on breast cancer mortality of a screening programme that involved an annual MRI scan from the age of 30, and additional annual mammographic x-rays from the age of 40 until the age of 73.

For women who showed no evidence of a strong hereditary risk, the group compared the effect on breast cancer mortality of 3 possible screening protocols:

- 18-monthly mammographic screening between the ages of 35 and 49, and then 3-yearly mammograms between the ages of 50 and 69
- 18-monthly mammographic screening between the ages of 40 and 49, and then 3-yearly mammograms between the ages of 50 and 69
- 18-monthly mammographic screening between the ages of 40 and 69

The working party used an upper age limit of 69 because the implementation of the age extension to the standard screening programme to cover women up to the age of 73 is subject to the results of the age extension trial which will take some years to complete.

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2.1.2. Methods

The methods used are summarised here, but full details are given in a paper by Berrington de Gonzalez and Reeves (2005)[4] and in a forthcoming paper by Parkin et al.[3]

For modelling purposes, Reeves et al. first estimated the number of radiation-induced breast cancer deaths associated with the proposed programmes. It was assumed that all mammographic screens consist of a 2-view screen, with an average radiation dose to the glandular breast tissue of 3.85 mGy.[5] It was also assumed that radiation-induced breast cancer risk can be described by an excess RR model, based on data from pooled analyses of previous cohort studies.[6]

Next, the number of breast cancer deaths that would be prevented by each of the proposed screening programmes was estimated, based on results from randomised clinical trials among women of various ages.[7,8] The overall RR of breast cancer mortality associated with invitation to screening is estimated at 0.84 (95% CI 0.77 to 0.91). For the purposes of these analyses, it was therefore assumed that, given full attendance for screening, 18-monthly screening in women aged 40 to 49 and 3-yearly screening in women aged 50 to 69 are associated with a 25% reduction in breast cancer mortality. A further assumption of the model was that a decreased interval of 18-months between screening episodes for women aged 50 to 69 is associated with a 30% reduction in mortality. The analysis assumed a lead time (the amount of time by which diagnosis is advanced as a result of screening) of 2 years, regardless of the age at which screening takes place.

To test the overall robustness of the findings, a number of sensitivity analyses were conducted. In order to address the uncertainty surrounding the mortality reduction associated with screening women under the age of 50, all analyses were repeated with the altered assumption that the mortality reduction in this age group is 20% rather than 25%. In view of the possible extension of the screening programme to women aged 47 to 73, analyses also considered the effect of commencing screening at age 47 rather than at age 50.

Results for each screening programme are presented according to the background risk of the disease in the screened population. It was assumed that RR in the target population is constant across a woman's lifetime, so that results can be applied generally and are not confined to populations defined by a specific risk factor.

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The primary measure of effectiveness in the modelling was the net change in breast cancer mortality achieved by each screening programme, as compared to standard screening. Results from the models were therefore compared to the number of women requiring screening (n=278) and the number of screens required (n=2000) in the routine NHSBSP in order to prevent one extra breast cancer death in the general population.

2.1.3. Results

2.1.3.1. Screening programmes aimed at women at moderately high risk of breast cancer (RR of 2 to 4)

Given a group of women with a RR of 3 (compared to the general target group for screening), screening according to the routine protocols of the NHSBSP would reduce the number of breast cancer deaths by 10.8 (3 x 3.6), see Table 1, however, 18-monthly screening from the age of 40 would reduce the number of breast cancer deaths by 13.5 (3 x 4.5). Therefore, the extended programme would prevent 2.7 extra deaths, though 371 women would need to undergo extended screening to prevent one additional death (as illustrated in Figure 1).

4.8 extra breast cancer deaths would be prevented by screening at 18-monthly intervals throughout the programme, and 208 women would need to undergo extended screening to achieve this result.

Table 1. Estimated effect on breast cancer mortality of various screening programmes per unit RR of breast cancer in the target population†

Screening programme	No. radiation-related breast cancer deaths per 1000 women screened	No. breast cancer deaths prevented per 1000 women screened	Net effect on no. of breast cancer deaths per 1000 women screened
3-yearly screening 50 to 69	0.1	3.7	-3.6
18-monthly screening from 35 to 49 followed by 3-yearly screening until 69	0.4	5.1	-4.7
18-monthly screening from 40 to 49 followed by 3-yearly screening until 69	0.3	4.8	-4.5

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†Estimates are based on the following assumptions: regular 18-monthly screening before the age of 50 and triennial screening between the ages of 50 to 69 are associated with a reduction in breast cancer mortality of 25%; deaths from radiation-related breast cancers diagnosed during the screening period are also proportionately reduced due to screening; women undergoing standard screening are assumed to have their first screen at an average age of 51, and women undergoing extended screening from age 35 or 40 are assumed to have their first screen at an average age of 36 or 41, respectively.

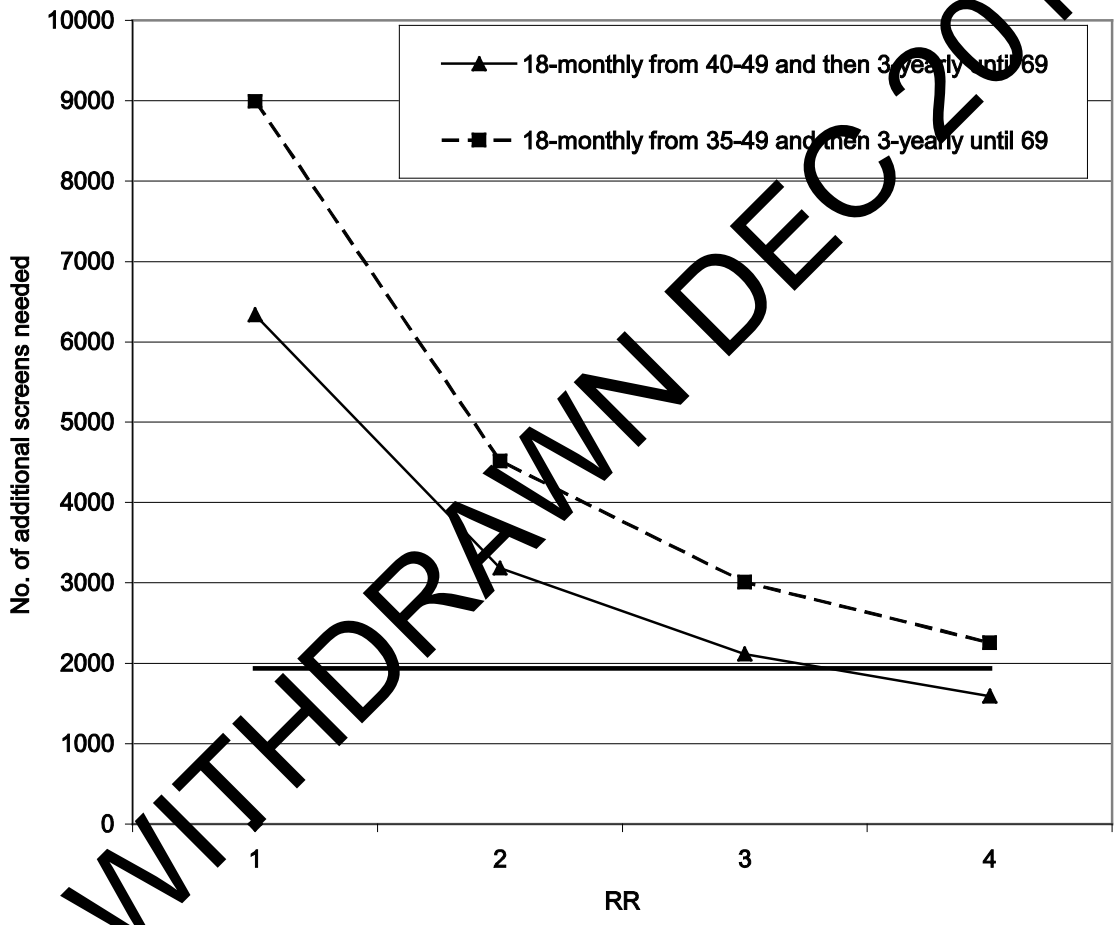

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Figure 1. Estimated number of women who would need to be screened, under alternative extended screening programmes, to avoid one extra breast cancer death relative to the standard programme.

* Solid horizontal line indicates the estimated number of women from the general population who need to be screened under the routine screening protocols in order to avoid one death.

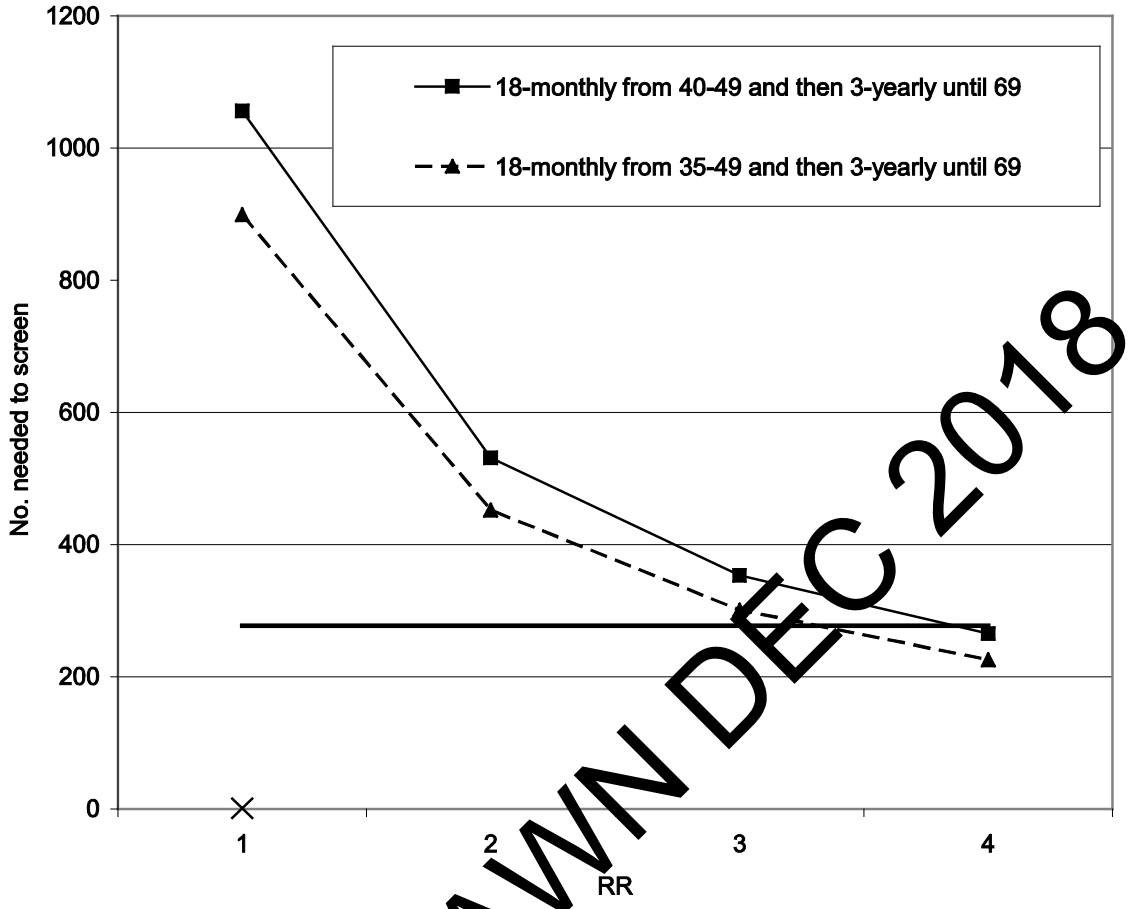

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Figure 2. Estimated number of additional screens needed, under alternative extended screening programmes, in order to avoid one extra breast cancer death relative to the standard programme.

* Solid horizontal line indicates the estimated number of women from the general population who need to be screened under the routine screening protocols in order to avoid one death.

2.13.2. Screening programmes aimed at women at very high risk of breast cancer (RR of 8):

The net benefits of a more intense screening programme for women at very high risk were also estimated. Table 2 shows that these would be substantial. Table 1 indicates that 29 breast cancer deaths would be prevented by following the standard screening programme in a group of women with a RR of 8, but even the most conservative estimates in Table 2 indicate that an extra 5 to 9 breast cancer

deaths would be avoided by implementing a more intense screening protocol for women at very high risk.

Table 2. Estimated risks and benefits associated with annual MRI/mammographic screening of women with a very strong hereditary risk of breast cancer (RR=8)†

Proposed protocol and assumed mortality reduction	No. of radiation-induced deaths per 1000 women screened	No. of breast cancer deaths avoided by screening per 1000 screened women	Net change in breast cancer deaths per 1000 screened women
<40 MRI : 20% 40 to 49 (xray+MRI):20% 50 to 73	4.4	39.0	-34.6
<40 MRI : 25% 40 to 49 (xray+MRI):25% 50 to 73	4.4	41.7	-37.3
<40 MRI : 30% 40 to 49 (xray+MRI):30% 50 to 73	4.4	44.3	-40.0
<40 MRI : 20% 40 to 49 (xray+MRI):20% 50 to 73	4.1	44.7	-40.6
<40 MRI : 25% 40 to 49 (xray+MRI):25% 50 to 73	4.1	47.3	-43.3
<40 MRI : 30% 40 to 49 (xray+MRI):30% 50 to 73	4.1	50.0	-45.9

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† Estimates of the numbers of radiation-induced breast cancer deaths assume that deaths from radiation-induced breast cancers diagnosed during the screening period are also proportionately reduced by screening; the standard screening programme is assumed to commence at an average age of 49.

2.2. High hereditary risk

2.2.1. Definition

Women in the 'very high risk' group (ie those who have a lifetime RR of breast cancer that is greater than 8 compared to the general target population for screening) eligible for enhanced surveillance under current NICE guidelines include:

1. Women where there is a very strong family history of breast cancer fulfilling strict risk criteria:

   From 30 to 39 years:

   - where women have a 10-year risk of greater than 8%

   From 40 to 49 years:

   - where women have a 10-year risk of greater than 20%
   - where women have a 10-year risk of greater than 12% where mammography has shown a dense breast pattern[9]

2. TP53, BRCA1, or BRCA2 mutation carriers.[9]

3. Women who have not been tested but who have a high chance of carrying a BRCA1 or TP53 mutation, if they are at:

   - a 50% risk of carrying a TP53 or BRCA1 mutation in a tested family
   - a 50% risk of carrying a TP53 or BRCA1 mutation from untested or inconclusively tested families with at least a 60% chance of carrying a BRCA1 or TP53 mutation (that is, a 30% risk of carrying one of these mutations themselves)[9]

4. Women in any of the above categories (1 to 3) with breast cancer, who therefore remain at highly increased risk of a new primary breast cancer and are eligible for enhanced breast surveillance if they have residual breast tissue.

5. Women over 50 years:

   Enhanced breast surveillance can be offered provided the strict risk criteria listed above (1 to 4) have been fulfilled.

   Women with a very high risk of breast cancer do not require breast surveillance if all of their breast tissue has been removed.

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2.2.2. Prevalence

The birth prevalence of the BRCA1 gene mutation is 0.07 to 0.09%. For BRCA2, birth prevalence is 0.14 to 0.22%.[10] These data suggest that there may be between 16,000 to 23,000 women aged between 30 and 49 years with these genetic mutations in the general population, however it is unlikely that all of the women who are carrying genetic mutations have been identified, and some women may not be able to be genetically tested. In 2006 it was estimated that ~2,500 women aged between 30 and 49 had been identified in England as being at very high risk of breast cancer, and hence eligible for increased surveillance.[9]

2.2.3. Penetrance of breast cancer

The breast cancer risk associated with BRCA1 or BRCA2 mutations varies widely, depending on the method used to identify cases for study. The lowest penetrance estimates are from population series of cases, which are unselected for family history,[11] however, analysis of patients referred to genetic services due to a strong family history of the disease[12] reveal levels of cumulative breast cancer risk that are similar to those estimated in kindreds identified in the Breast Cancer Linkage Consortium Cohort (BCLC).[13,14,15,16] Both the presence of modifier alleles in high-risk families and shared environmental factors account for the variation in breast cancer penetrance between different groups.[17]

Table 3. Cumulative risk of breast cancer by 70 years for BRCA1 and BRCA2

	Cumulative risk of breast cancer in *BRCA1* by the age of 70	**Cumulative risk of breast cancer in *BRCA2* by the age of 70**
Meta-analysis of population case series	65% (95% CI 44-78%)[11]	45% (95% CI 31-56%)[11]
Clinical genetics services	68% (95% CI 65-71%)[12]	75% (95% CI 72-78%)[12]
Breast Cancer Linkage Consortium	87% (95% CI 72-95%)[16]	84% (95% CI 43-95%)[13]

A study of 385 apparently unrelated families referred to clinical genetic services in England found 223 families who were BRCA1 carriers, and 162 who were BRCA2 carriers. The researchers calculated that the annual incidence of breast cancer in BRCA1 and BRCA2 mutation carriers is ~2% from 30 to 79 years of age.[12] Of those women who developed breast cancer, only 1% of cases in BRCA1 carriers

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and 2% of cases in BRCA2 carriers were DCIS, and 15/16 of the total number of women with DCIS developed it before the age of 60. The incidence of breast cancer in BRCA1 and BRCA2 carriers has increased in recent birth cohorts, in line with population trends.

The penetrance for breast cancer by age for women who are BRCA1 or BRCA2 carriers is shown in Table 4.[12]

Table 4. Penetrance for breast cancer by age

Cancer risk to age	*BRCA1* breast (standard error)	*BRCA2* breast (standard error)
30	2%	2.5%
40	16.5% (0.015)	17% (0.019)
50	48% (0.023)	42% (0.027)
60	55% (0.027)	63% (0.031)
70	68% (0.033)	75% (0.033)
80	79.5% (0.04)	88% (0.037)

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Thus, by the age of 50, there is a 48% cumulative risk of breast cancer in women who carry the BRCA1 mutation and a 42% cumulative risk in women who carry BRCA2. The peak decade for breast cancer diagnosis in women who have these mutations is between the ages of 40 and 50 for both BRCA1 and BRCA2 carriers.[12]

2.2.4 TP53

In a series of 494 tumours diagnosed in 226 confirmed or obligate TP53 mutation carriers, the median age of breast cancer diagnosis was 33 years.[18] Most cases occurred in women aged 30 to 40. In another series, 32% of breast cancers occurred before the age of 30, and no cases occurred after the age of 50.[19] Therefore, the majority of breast cancers in these women occurred before the menopause (before the age of 50).

2.2.5. Multiple primary breast cancer

Where women with BRCA1 or BRCA2 mutations are diagnosed with breast cancer, there is an increased risk of a new primary breast cancer occurring. This risk has been quantified: BRCA1 carriers between the ages of 30 and 70 have an average 2.6% per annum risk, while BRCA2 carriers have an average 1.8% per annum risk over the same age range (D. Easton, personal communication based on data from the Breast Cancer Linkage Consortium).[13,15]

Cases with TP53 mutations are at increased risk of multiple primary cancers, including breast cancer. In one series, 22/52 (42.3%) of TP53 mutation carriers developed at least 2 primary tumours.[20] This confirms the need for continued surveillance after a primary breast cancer is diagnosed if residual breast tissue remains.

2.2.6. Summary

Patients at very high risk of breast cancer (ie those with a RR of 8 or greater compared to the general population) have a constant and increased risk of multiple primary breast cancers from an early age (from age 20 with TP53 and age 30 with BRCA1 and BRCA2). In BRCA1 and BRCA2 cases, the annual incidence of primary breast cancer is ~2% between 30 and 79 years of age. Therefore, patients at 50% risk of BRCA1 mutation (or from equivalent high-risk families) will have at least a 1% per annum risk of breast cancer between the ages of 30 and 79 years.

2.3. Epidemiological risk factors

The group considered the effects of parity, age at menopause, hormone use, breast density, alcohol consumption, obesity, and benign breast disease on breast cancer risk.[3] Benign breast disease was treated as an entity, but it should be noted that some states of benign conditions can be considered to be directly premalignant (see 2.4, below). 'Age at menopause' is a particularly difficult risk factor to use in the context of screening, since (by definition) it will be identified late. Therefore, only combinations of the 6 risk factors remaining when age at menopause was excluded were taken to imply a RR of greater than 3.

Table 5, which uses data from a forthcoming paper,[3] stratifies the population by age and RR (the latter determined by parity, hormone use, breast density, alcohol consumption, obesity, and a previous history of benign breast disease). For each subgroup, it shows the risk over the next 10 years, the percentage of the population subject to that risk, and the percentage of cancers. The cutoffs for the

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group with an RR between 1.9 and 3.6 were chosen to correspond with a lifetime risk up to the age of 74 of between 17% and 30% (a woman who has a first-degree relative with breast cancer has a lifetime risk of 17%, whereas a woman who has a strong family history of breast cancer has a lifetime risk of over 30%). The underlying assumptions behind the calculations are that the risk factors are independent in their prevalence (with the exception of breast density and BMI) and that the RRs act multiplicatively, and do not interact to affect the age-specific rates. The data for density were adjusted for the known association between breast density and BMI.[3]

Table 5 shows that, at age 40, about 9 per 10,000 women have a RR of 3.6 or greater, compared to the general target population for screening. These women will all have a history of benign breast disease and will have a breast density of at least 50% (the vast majority will have a breast density of greater than 75%, with one or more additional markers of risk, eg moderate or heavy alcohol consumption, use of combined oral contraceptives, or nulliparity). Around 15 per 10,000 women at age 40 have an RR of 3.0 or greater with similar combinations of risk factors.

About 3.9% of women aged 40 have a RR of 1.9 or greater compared to the general population, and this group accounts for about 9.5% of breast cancers at this age. Of the women in this group, 90% have a history of benign breast disease and breasts with a density of at least 50%. Women with benign breast disease, who are current users of combined oral contraceptives, and who are moderately heavy consumers of alcohol also fall into this category, as do a few women with very dense breasts (over 75%) and at least 2 further risk factors, eg moderate to heavy alcohol consumption, current use of combined oral contraceptives, and nulliparity. (As previously mentioned, several breast cancer risk factors remain unknown until after the age of 40).

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Table 5. Stratification of the population into risk categories based on parity, hormone use, breast density, alcohol consumption, obesity, and benign breast disease.

Age		RR<0.8	RR 0.8-1.2	RR 1.2-1.9	RR 1.9-3.6	RR >3.6
40	Risk over next 10 years	1.0%	1.5%	2.2%	3.6%	6.2%
40	Percentage of population	48.1	28.3	19.8	3.8	0.1
40	Percentage of cancers	33.8	28.2	28.5	9.2	0.3
55	Risk over next 10 years	2.3%	3.1%	4.4%	7.0%	11.9%
55	Percentage of population	47.1	28.6	19.6	4.4	0.2
55	Percentage of cancers	32.6	28.0	28.0	10.5	1.0
70	Risk over next 10 years	2.5%	3.1%	5.2%	8.0%	16.7%
70	Percentage of population	41.1	27.6	16.2	4.6	0.5
70	Percentage of cancers	29.3	3[illegible]	24.4	10.6	2.5

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At age 55, 0.3% of women will have risk factors that give them a RR of 3.6 or greater compared to the general population, and this group accounts for 1.2% of all breast cancers diagnosed at that age. About 1.7% of women in this age category will have a RR of greater than 3. These women will have at least 4 different risk factors for breast cancer out of the list of 6 factors described, and virtually all of them will have a history of benign breast disease.

About 4.6% of women aged 55 have an RR of greater than 1.9, accounting for 11.5% of breast cancers at this age. Almost all of these women will either have a history of benign breast disease or be current users of HRT.

With regard to familial breast cancer, 10% to 12% of screened women have a sister or a mother with breast cancer, and, on average, these women have a RR of 2 compared to the general population. If we assume multiplicative risk, women with this family history will reach a RR of around 4 once other risk factors (entailing a RR of 1.9 or more) are taken into account (see Table 1). Women who have a RR of

3 or greater due to epidemiological risk factors (with or without a family history of breast cancer) are estimated to constitute a maximum of 6% of the female population in any of the age groups from 40 to 70 years of age.

2.4. Benign breast disease and premalignant conditions

Several observational studies show that women with atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ have a risk of developing breast cancer that is 3 to 5 times greater than that of the general population.[21,22,23,24,25,26,27,28] The bulk of the evidence suggests that this group has a RR of greater than 4. The risk is not restricted to the breast where the biopsy or excision of the benign condition (atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ) occurred, and surveillance programmes must not focus on one breast only.

The elevated level of risk for these women is not significantly altered by a family history of breast cancer,[26,28] but there is evidence that the woman's age at diagnosis of a premalignant lesion, the type of lesion and the time that has elapsed since her biopsy do modify the level of risk,[28] however, these data are partly conflicting and have not, at present, been shown to affect the risk estimates to an extent that would affect decisions about surveillance.

2.5. Supradiaphragmatic irradiation at age below 30

Women who have undergone SDI before the age of 30 with a breast dose of greater than 4 Gy are estimated to have a RR of 8 or greater for breast cancer.[29,30,31,32] The risk is reduced if doses of >5 Gy were given to the ovaries, or if more than 4 courses of chemotherapy with alkylating agents were given,[31] however, these factors would only reduce the risk to a level well below 8 in women irradiated after the age of 25.[31,32] The RR estimates provided are for SDI given after the age of 30.

Where women received SDI before the age of 17, the programme for women with a RR of greater than 8 should start at age 25.

2.6. HTA document on surveillance after breast cancer treatment

The HTA's findings show that surveillance with mammography adds survival benefit by enabling early detection of ipsilateral breast recurrences and

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metachronous contralateral breast cancer.[2] The annual rate of these 2 occurrences is similar over at least 10 years of follow-up.

Practices for mammography surveillance vary considerably, and the effectiveness of the programmes currently in use has not been systematically tested (a literature search conducted by the HTA found no randomized controlled trials and only 9 observational studies of varying quality, none of which directly examined any of the common practices of today).

Looking at Table 5, it follows that a RR of around 4 compared to the general population would indicate an annual breast cancer risk of 1% or more. The combined risk of an ipsilateral breast recurrence and a metachronous contralateral breast cancer would amount to more than 1% annually for many women who had previously treated with breast cancer.

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3.Conclusions

3.1. Screening programmes

The working party proposes the following screening routines:

Women with an RR<3 compared to average risk	Women at RR 3-8 compared to average risk	Women at RR≥8 compared to average risk
Routine programme	X-ray mammography over age range 40 to 73 at an 18-monthly interval.	According to proposed high-risk surveillance protocols for the NHSBSP

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It is important to note that it will not be possible to establish the level of risk for the majority of women who will be found to have a RR between 3 and 7 before the age of 40. These women will therefore commence their screening routine well after the point identified in the above table.

The working party acknowledges that there are 3 major difficulties in providing evidence to underpin these recommendations:

- the fact that there is little randomised data available for many of the underlying determinants of an effective screening programme
- the fact that the models estimating screening's effects are sensitive to assumptions
- the fact that programmes would ideally be based on substantially more knowledge about their performance in relation to tumour biology

The modelling indicates that the main benefit from the extended programme is derived from 2 things: the extension of the lower age limit and the inclusion of women who have an RR of greater than 3.5 or 4. This level of risk is commensurate with the number of women (n=278) who need to be screened and the overall number of screens required (n=2000), in the standard NHSBSP screening protocol to prevent one breast cancer death in the general population, however, the working party chooses to recommend a RR of 3 as the cut-off, and an 18-month screening interval. The more intensive protocol is designed to err on the side of inclusivity, given the uncertainties involved, while complying with the remit to design logistically deliverable programmes. Following this protocol should

achieve at least the same magnitude of benefit for women at high risk of breast cancer as the routine programme obtains for women at average risk.

In addition to the proposed high-risk surveillance protocols for the NHSBSP, which were designed by the ACBCS in May 2011, the working party recommends baseline mammography for women entering the programme. Where MRI is recommended before the age of 50, the radiology team should assess the necessity of continuing with this type of imaging after the woman reaches 50 on the basis of her mammographic density.

3.2. Identification of risk groups

The working party assumes that there will be no screening at an early age (ie before the age of 30) to detect risk factors. Risk categories will therefore be identified in many different clinical settings, with the result that many women may only be recognized as candidates for high-risk screening after they reach the starting age for the routine screening programme.

3.2.1. Women with high hereditary risk (RR 3 to 8 or ≥8)

Identification and risk stratification will occur through evaluation at clinical genetics services. Women will then be referred to the screening programme as appropriate.

3.2.2. Women with high risk as defined by epidemiological risk factors (RR 3 to 8)

If a specific programme for screening these women becomes a priority, a mechanism to identify them will be needed. One possible trigger for further evaluation of risk (eg by interview) is a history that includes an operation for benign breast disease. Another is detection of high density on a mammogram.

3.2.3. Women with atypical ductal or lobular hyperplasia and women with lobular carcinoma in situ (RR 3 to 8)

These women can be identified as candidates for high-risk surveillance at a follow-up visit for information about the histopathological results of a biopsy or extirpation.

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3.2.4. Women at high risk after receiving SDI before age of 30 (RR ≥8)

This group can be identified at departments and clinics treating and following women after SDI. The identification should ideally include estimated dose to the breasts, age at therapy, and modifying factors (dose to ovaries and treatments with chemotherapy).

3.2.5. Women with a previously treated breast cancer who have a 1% or greater annual risk of ipsilateral or contralateral new breast events (RR 3 to 8)

The working party recommends that a clinical working party is set up to investigate ways of identifying these women at the point when all postoperative information is evaluated, eg when follow-up is decided at a multidisciplinary team meeting.

3.3. Alignment of screening recommendations

The working party recommends that this report is considered when the recommendations are revised for women with a strong hereditary risk and for women who have been treated with mantle radiotherapy. Different screening initiatives should be coordinated.

3.4. Level of risk required when new risk factors are considered

The findings of this report imply that any new risk factor that is to be considered as a means of defining a group of women eligible for a special screening programme should be associated with a RR of 3 or greater.

3.5. Population effect

The high-risk groups identified in this report involve a relatively small proportion of all women targeted for screening. Therefore, the gains in screening's effectiveness for these groups will impact only marginally on the overall performance of the screening programme. The majority of breast cancers will still be diagnosed in women with an average or low risk. It should be noted that the models in this report imply that a large part of the benefit of high-risk surveillance results from screening women after the age of 50.

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3.6. New developments, eg using MRI as screening tool

When new data about the performance of different screening tools or about tumour biology are available, these recommendations will need to be reviewed. There is an especially urgent need to incorporate new developments in the use of MRI for breast screening.

3.7. Evaluation of programmes

The working party recommends that the programmes outlined in this report are prospectively monitored. This means registering women for a more intensive programme, recording the reason for including them in the high-risk screening programme, and detailing the type of programme implemented. Attendance, breast cancer prevalence at screens, breast cancer incidence between screens, mode of detection, stage distribution by mode of detection, treatments given, and breast cancer mortality should all be evaluated.

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