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Abstract

The clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer: systematic reviews, registry database analyses and economic evaluation

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Background: Following primary breast cancer treatment, the early detection of ipsilateral breast tumour recurrence (IBTR) or ipsilateral secondary cancer in the treated breast and detection of new primary cancers in the contralateral breast is beneficial for survival. Surveillance mammography is used to detect these cancers, but the optimal frequency of surveillance and the length of follow-up are unclear.
Objectives: To identify feasible management strategies for surveillance and follow-up of women after treatment for primary breast cancer in a UK setting, and to determine the effectiveness and cost-effectiveness of differing regimens.
Methods: A survey of UK breast surgeons and radiologists to identify current surveillance mammography regimens and inform feasible alternatives; two discrete systematic reviews of evidence published from 1990 to mid 2009 to determine (i) the clinical effectiveness and cost-effectiveness of differing surveillance mammography regimens for patient health outcomes and (ii) the test performance of surveillance mammography in the detection of IBTR and metachronous contralateral breast cancer (MCBC); statistical analysis of individual patient data (West Midlands Cancer Intelligence Unit Breast Cancer Registry and

Edinburgh data sets); and economic modelling using the systematic reviews results, existing data sets, and focused searches for specific data analysis to determine the effectiveness and cost–utility of differing surveillance regimens.

Results: The majority of survey respondents initiate surveillance mammography 12 months after breast-conserving surgery (BCS) (87%) or mastectomy (79%). Annual surveillance mammography was most commonly reported for women after BCS or after mastectomy (72% and 53%, respectively). Most (74%) discharge women from surveillance mammography, most frequently 10 years after surgery. The majority (82%) discharge from clinical follow-up, most frequently at 5 years. Combining initiation, frequency and duration of surveillance mammography resulted in 54 differing surveillance regimens for women after BCS and 56 for women following mastectomy. The eight studies included in the clinical effectiveness systematic review suggest surveillance mammography offers a survival benefit compared with a surveillance regimen that does not include surveillance mammography. Nine studies were included in the test performance systematic review. For routine IBTR detection, surveillance mammography sensitivity ranged from 64% to 67% and specificity ranged from 85% to 97%. For magnetic resonance imaging (MRI), sensitivity ranged from 86% to 100% and specificity was 93%. For non-routine IBTR detection, sensitivity and specificity for surveillance mammography ranged from 50% to 83% and from 57% to 75%, respectively, and for MRI from 93% to 100% and from 88% to 96%, respectively. For routine MCBC detection, one study reported sensitivity of 67% and specificity of 50% for both surveillance mammography and MRI, although this was a highly select population. Data set analysis showed that IBTR has an adverse effect on survival. Furthermore, women experiencing a second tumour measuring >20 mm in diameter were at a significantly greater risk of death than those with no recurrence or those whose tumour was <10 mm in diameter. In the base-case analysis, the strategy with the highest net benefit, and most likely to be considered cost-effective, was surveillance mammography alone, provided every 12 months at a societal willingness to pay for a quality-adjusted life-year of either £20,000 or £30,000. The incremental cost-effectiveness ratio for surveillance mammography alone every 12 months compared with no surveillance was £4727.

Limitations: Few studies met the review inclusion criteria and none of the studies was a randomised controlled trial. The limited and variable nature of the data available precluded any quantitative analysis. There was no useable evidence contained in the Breast Cancer Registry database to assess the effectiveness of surveillance mammography directly. The results of the economic model should be considered exploratory and interpreted with caution given the paucity of data available to inform the economic model.

Conclusions: Surveillance is likely to improve survival and patients should gain maximum benefit through optimal use of resources, with those women with a greater likelihood of developing IBTR or MCBC being offered more comprehensive and more frequent surveillance. Further evidence is required to make a robust and informed judgement on the effectiveness of surveillance mammography and follow-up. The utility of national data sets could be improved and there is a need for high-quality, direct head-to-head studies comparing the diagnostic accuracy of tests used in the surveillance population.

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Contents

List of abbreviations

ABS at BASO	Association of Breast Surgeons at the British Association of Surgical Oncology
BCS	breast-conserving surgery
BCT	breast-conserving therapy
CE	clinical examination
CI	confidence interval
CT	computerised tomography
ER	oestrogen receptor
DOR	diagnostic odds ratio
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
FFDM	full-field digital mammography
GP	general practitioner
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRT	hormone replacement therapy
HSRU	Health Services Research Unit
IBTR	ipsilateral breast tumour recurrence
ICER	incremental cost-effectiveness ratio
MCBC	metachronous contralateral breast cancer
MRI	magnetic resonance imaging
NHSBSP	NHS Breast Screening Programme
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NR	not reported
OR	odds ratio
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
RCR	Royal College of Radiologists
RCT	randomised controlled trial
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SIGN	Scottish Intercollegiate Guidelines Network
US	ultrasound
WMCIU	West Midlands Cancer Intelligence Unit
XRM	X-ray mammography

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Survival following breast cancer treatment is increasing. A key question is, therefore, how best to follow up patients after completion of primary treatments. There is considerable debate about the role and optimal organisation of the follow-up of patients following treatment for primary breast cancer. Data indicate that the early detection of ipsilateral breast tumour recurrence or ipsilateral second primary cancer [ipsilateral breast tumour recurrence (IBTR)] in the treated breast and detection of new primary cancers in the contralateral breast [metachronous contralateral breast cancer (MCBC)] is beneficial in terms of survival. This raises the question as to how best to identify ipsilateral local recurrence of disease and new contralateral primary breast cancer at the earliest possible stage. Surveillance mammography is directed towards the detection of IBTR and MCBC. However, the optimal frequency of mammographic surveillance and the length of follow-up are unclear.

Objectives

1. Identify feasible management strategies for surveillance and follow-up of women after treatment for breast cancer in a UK setting.
2. Determine the effectiveness of differing surveillance and follow-up regimens after treatment for breast cancer.
3. Estimate the costs of differing surveillance and follow-up regimens after treatment for breast cancer.
4. Estimate the cost-effectiveness of differing surveillance and follow-up regimens after treatment for breast cancer.
5. Identify future research needs.

Methods

The work comprised a survey of UK breast surgeons and radiologists to identify current UK surveillance mammography regimens and inform feasible alternative regimens. In addition, we undertook two discrete systematic reviews to determine the clinical effectiveness of differing surveillance mammography regimens carried out after treatment for primary breast cancer on patient health outcomes and the test accuracy of surveillance mammography in the detection of IBTR and MCBC. Sensitive search strategies of several major bibliographic databases were conducted from 1990 to mid 2009. We undertook statistical analysis of individual patient data [West Midlands Cancer Intelligence Unit (WMCIU) Breast Cancer Registry and Edinburgh data sets] and economic modelling using the systematic reviews results, existing data sets, and focused searches for specific data analysis to determine the effectiveness and cost–utility of differing surveillance regimens. We developed an economic model in the form of a Markov model to represent the alternative surveillance regimens modelled at varying surveillance intervals. Parameter estimates for the Markov model were determined from a survey of existing data sets, a series of systematic reviews, and focused searches for specific data.

Results

Survey

We received responses from 17% (183/1048) of those surveyed, 64% were surgeons and 35% radiologists and were based in 105 NHS trusts across the UK. The majority initiate surveillance mammography 12 months post surgery for women who have had breast-conserving surgery (BCS) (87%) and for women who have had a mastectomy (79%). Annual surveillance mammography was the most commonly reported surveillance mammography frequency for women after breast-conserving surgery (BCS) or after mastectomy (72% and 53%, respectively), with biennial mammography the next most frequently reported (12% and 30%, respectively). Most (74%, 136/182) discharge women from surveillance mammography and they do this most frequently 10 years after surgery. The majority (82%, 148/180) do discharge from clinical follow-up and most frequently at 5 years. Just over half (55%, 98/179) responded that they discharge women to the NHSBSP if eligible. Combining initiation, frequency and duration of surveillance mammography resulted in 54 differing surveillance regimens for women after BCS and 56 for women following mastectomy. The most commonly followed four regimens for women after BCS or after mastectomy are to initiate surveillance mammography 12 months after surgery, conduct annual surveillance mammography with indefinite duration (12%, 19/154, 7%, 10/136 respectively); or discharge from both clinical and mammographic surveillance at 5 years (14%, 22/154, 10%, 13/136 respectively); or 10 years (12%, 18/154, 11%, 15/136 respectively) after surgery or discharge from clinical follow-up at 5 years with continued mammographic surveillance until 10 years (13%, 20/154, 8%, 11/136 respectively). Our findings suggest that, although common patterns in surveillance mammography practice exist, there is considerable variation in the combinations of start, frequency, duration and discharge from surveillance mammography. Our findings reflect the different guidance given by the various professional organisations with an interest in surveillance after breast cancer, in combination with the local protocols of the respondents.

Systematic reviews

Eight studies, involving 3775 women, were included in the systematic review of clinical effectiveness. Although none of the tests of interest was used for the same purpose (i.e. routine or non-routine surveillance) in all studies, results suggest that the use of surveillance mammography offers a survival benefit compared with a surveillance regimen that does not include surveillance mammography.

Nine studies, involving 3724 women, were included in the systematic review of test performance. For the detection of IBTR in routine surveillance where there was no prior suspicion of recurrence, the highest sensitivity was shown for magnetic resonance imaging (MRI) and combined MRI/clinical examination at 100%, whereas the highest specificity was shown for surveillance mammography alone (97%) although this was obtained in a highly select population. Clinical examination alone had the lowest sensitivity (50%) and surveillance mammography with clinical examination had the lowest specificity (67%). For the detection of IBTR in patients for whom there was a suspicion of recurrence, sensitivity of tests varied from 50% (surveillance mammography) to 100% (MRI) and specificity ranged from 31% (ultrasound) to 96% (MRI). In the detection of MCBC in routine surveillance, sensitivity ranged from 0% (clinical examination) to 100% for the combination of surveillance mammography, clinical examination, ultrasound and MRI. Specificity ranged from 50% for surveillance mammography, MRI or clinical examination to 99% for the combination of surveillance mammography and ultrasound. Again, the highly selected nature of the population should be borne in mind in the context of these results.

Analyses of the WMCIU and Edinburgh data sets

The analyses showed that IBTR has an adverse effect on survival that is independent of known risk factors. Furthermore, in those women experiencing a second tumour (either IBTR or MCBC) the size of this second tumour is important, with those women with tumours of > 20 mm in diameter being at a significantly greater risk of death than those with no recurrence or those whose tumour was < 10 mm in diameter.

Economic evaluation

The results of the economic model should be considered exploratory and interpreted with caution given the paucity of data available to inform the economic model. In the base-case analysis, the strategy with the highest net benefit, and therefore the most likely to be considered cost-effective, was surveillance mammography alone, provided every 12 months at a societal willingness to pay for a quality-adjusted life-year (QALY) of either £20,000 or £30,000. The incremental cost-effectiveness ratio for surveillance mammography alone every 12 months compared to no surveillance was £4727. This result holds for women previously treated for their primary cancer with either breast-conserving surgery or mastectomy or for women who suffer IBTR. The results of the model are sensitive to changes in the incidence of recurrent cancer. When the expected incidence is increased towards the maximum that could be expected (approximately 0.008 per annum) clinical surveillance plus mammography has an incremental cost per QALY of approximately £30,000. As the surveillance interval and incidence increase regimens that are more costly but more effective (proxied by the MRI plus clinical surveillance) may also have incremental costs per QALY < £30,000. This suggests that there may be some scope for research into alternative technologies that could be used for surveillance.

We did not conduct probabilistic sensitivity analysis due to statistically imprecise and limited data. We did conduct both one-way and multiway sensitivity analyses, however. Sensitivity analysis included varying the probability of cancer, inflating the risk of death from cancer, inflating the risk of cancer progression in undiagnosed or untreated cancers, varying diagnostic accuracy of the surveillance tests and varying costs and age.

The results of the model were sensitive to incidence and other factors, for example age, tumour characteristics, etc., which might define women with greater or lesser likelihoods of developing an IBTR or MCBC. These results suggest that a more intensive follow-up of women with greater likelihood of IBTR or MCBC may be worthwhile. Conversely, for women with less likelihood of IBTR or MCBC it may be more cost-effective for surveillance to be performed less often (every 2 or 3 years) with mammography alone. As the surveillance interval and incidence increase, strategies that are more costly, but more effective, may also have incremental costs per QALY below typical threshold values.

Limitations

Despite considerable and rigorous methods adopted for both systematic reviews, we found few studies meeting our inclusion criteria, none of which were a randomised controlled trial (RCT). The limited and variable nature of the data available precluded any quantitative analysis. There was no useable evidence contained in the Breast Cancer Registry database to assess the effectiveness of surveillance mammography directly. As few data were available, the economic results need to be treated cautiously. In particular, a series of simplifying assumptions were made about disease progression and prognosis of recurrent cancers. We took care to err on the side of caution when making these assumptions, however, in order to minimise the possibility of overestimating the value of surveillance. Furthermore, few data relevant to the UK were available on health-state utilities. We assumed that the data used were applicable to the UK and the health states modelled.

Conclusions

Implications for service provision

Surveillance is likely to improve survival, with a strategy of mammography alone, every 12–24 months, appearing to have the highest net benefits. The evidence base on which to recommend any change in current practice is relatively weak, however. Careful consideration should be given to stratification of patients to ensure maximum benefit to ensure optimal use of resources, with those women with a greater likelihood of developing IBTR or MCBC being offered more comprehensive (e.g. mammography and clinical follow-up) and more frequent surveillance (every 12 months). The greatest net benefit for women with the lowest likelihood of IBTR or MCBC is mammography only every 3 years. Although there may be arguments for delivering a varying surveillance regimen this would present challenges and, without provision of information and reassurance, might be a source of unnecessary anxiety for patients.

Suggested research priorities

■ The utility of the national data sets could be improved. In addition to the nationally agreed collection, it would be extremely valuable to record details of mode of detection for IBTR or MCBC; the frequency of the clinical and mammographic surveillance regimens, and how this varies over time; and whether a woman's IBTR or MCBC was detected during routine surveillance or as a result of it causing symptoms for the patient.

■ There is a need for high-quality, direct head-to-head studies comparing the diagnostic accuracy of tests used in the surveillance population. Further primary work should also consider whether the use of existing technologies, such as MRI, which may have better performance, could be worthwhile for patients at high risk of IBTR or MCBC. An economic analysis should form part of such work.

■ Further economic evaluation modelling should compare differing mixed regimens of clinical follow up, delivered in lower cost settings, combined with surveillance mammography in the long term. This would be important to inform further primary research (e.g. an RCT) which could then focus on regimens that appeared most promising.

■ A definitive RCT would be ideal and, although costly, could focus on those women at higher risk of IBTR or MCBC. The interventions considered might include mammography and MRI, for those at the highest risk, or surveillance mammography of 1 year versus a longer time interval, for example 3 years. Such a trial might also compare more sophisticated surveillance regimens, which vary not only in terms of the frequency of mammography but also in terms of the frequency and setting of clinical follow-up. An economic evaluation should form part of any RCT.

Funding

Chapter 1

Background

Description of health problem

Breast cancer affects one in nine women in the UK. At present, the 5-year survival rate in the UK is 82%. It is estimated that there are > 550,000 women who are alive and have been treated for breast cancer in the UK, which represents 2% of the total female population.[1] Survival following breast cancer treatment is increasing and a key question is how these patients should be followed up after completion of treatment for primary breast cancer. Surveillance mammography is directed towards the detection of ipsilateral breast tumour recurrence or ipsilateral second primary cancer (IBTR) in the treated breast and detection of new primary cancers in the contralateral breast [metachronous contralateral breast cancer (MCBC)]. In addition, follow-up of patients after treatment for primary breast cancer is aimed at detection of regional recurrence in the chest wall (following mastectomy) and axillae, detection of metastatic disease, and monitoring for side effects of adjuvant treatments and making changes in treatment where appropriate, together with psychological support and treatment as required.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of data from randomised controlled trials (RCTs) demonstrated that IBTR is associated with an adverse effect on survival in patients undergoing a variety of standard treatments for breast cancer. This may take up to 15 years to become evident, however.[2–4] Lu[5] recently conducted a systematic review to determine the impact of early detection of isolated locoregional and contralateral recurrence on survival. The author reported better overall survival for recurrences detected by mammography or in asymptomatic patients, with an absolute reduction in mortality of 17–28% if all breast cancer recurrences are detected early. Similarly, an analysis of the Surveillance, Epidemiology, and End Results (SEER) database reporting on 174,453 women who had previously been treated for a primary breast cancer demonstrated that, for women with MCBC with stage 0–I disease, there was an 81% reduction in breast cancer mortality compared with that of women who were identified with more advanced contralateral disease.[6] Therefore, the data suggest that the early detection of IBTR and of MCBC is beneficial in terms of survival. This raises the question as to how best to identify IBTR and MCBC.

Aetiology, pathology and prognosis

It is now generally accepted that IBTR has an adverse influence on patient survival. There is, however, no general agreement on the best treatment regimen for those who have experienced an IBTR.[7] Furthermore, it is not clear whether IBTR itself increases the risk of the development of distant metastases, or whether IBTR and risk of distant disease is merely a reflection of the original aggressiveness of the tumour with its resultant effect on survival.

Younger women (defined as those < 35 years of age), extensive ductal carcinoma in situ, excision margins involved with tumour and lymphovascular invasion by tumour are well recognised risk factors for IBTR.[8] Tumour size, grade and nodal involvement are risk factors for both local and distant recurrence.[9] Of patients experiencing IBTR, 40–50% will have further recurrence or
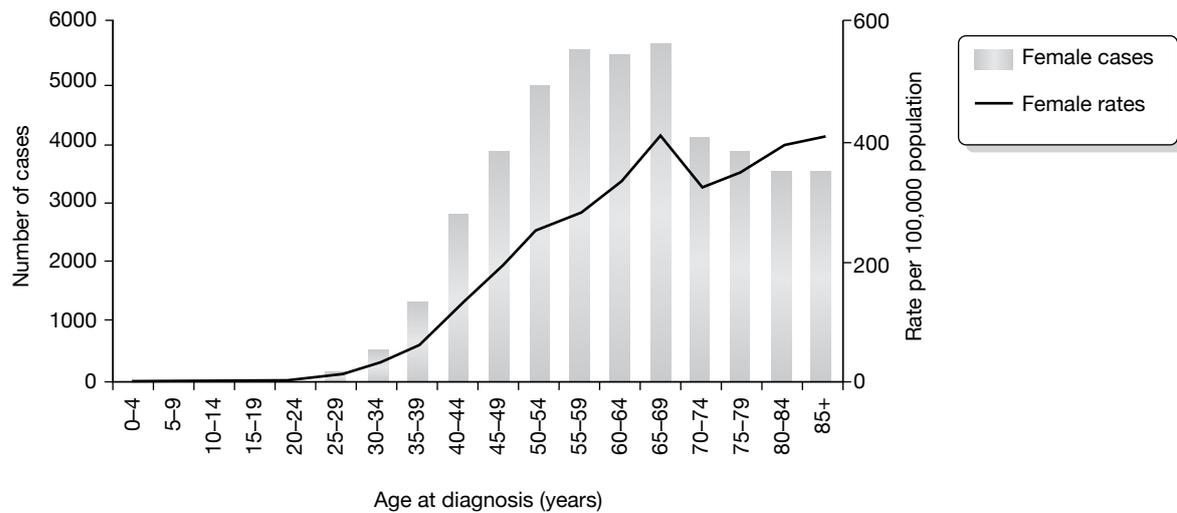
FIGURE 1 Number of new cases and age-specific incidence rates for female breast cancer, UK 2006. Reproduced with permission from Cancer Research UK.[14]

develop distant disease subsequently, particularly if the local recurrence occurs within 2 years of the initial presentation and treatment.[10]

Epidemiology

Breast cancer is an age-related disease, with 81% of cases occurring in those over 50 years of age. It is more prevalent in affluent societies, with the highest incidence being in North America and Western/Northern Europe. In those areas and countries, the most deprived socioeconomic groups have a lower incidence compared with the most affluent groups. Women who migrate from countries with a low incidence to those with a high incidence (e.g. Japan to the USA) often increase their risk, suggesting a strong effect for lifestyle and/or environmental factors. Early menarche, late menopause, oral contraceptive use, later age at first pregnancy, lower parity, lack of breastfeeding and use of hormone replacement therapy (HRT) after the age of 50 years are all recognised risk factors for breast cancer development. Following the publication of the Women's Health Initiative trial in 2002[11] there was a marked reduction in the use of HRT, which has resulted in a reduction of breast cancer incidence in the over-50-years age group.[12] In the UK, approximately 25% of women in the 45- to 69-year age group were using HRT by 2001 but this had fallen by half by 2006. This is estimated to have resulted in a reduction of around 1400 cases of breast cancer in the 50- to 59-year age group.[13]

Incidence and prevalence

There are 45,822 new cases of breast cancer in the UK each year.[14] *Figure 1* details Cancer Research UK incidence rates for women by age for 2006 in the UK. Approximately 20% of patients will develop a systemic recurrence and die within 5 years. In patients who undergo breast-conserving therapy (BCT), IBTR occurs in 1–2% of patients each year[15] and MCBC occurs at a rate of up to 0.8% each year.[16,17]

Around 550,000 women were living in the UK with a diagnosis of breast cancer in 2008.[18]

Impact of health problem

Significance for patients in terms of ill health

Ipsilateral breast tumour recurrence and MCBC have significant adverse effects on the patient. Further treatment is required and this often necessitates mastectomy for the patient who has a previously conserved breast together with the consideration of the use of systemic treatments (chemotherapy, hormone therapy, biological therapy). Disease recurrence has a significant adverse impact psychologically with major implications for the patient, their health and quality of life. There are data to indicate that patients who experience local disease recurrence have a poorer survival than those who do not have local recurrence.[2,7]

Significance for the NHS

The significance to the NHS in terms of the provision of clinical and mammographic surveillance, and treatment of IBTR and MCBC, is great. Following the treatment of primary breast cancer, patients are followed up with regular clinical examinations and surveillance mammography carried out at intervals as described below. Subsequent investigations are carried out to confirm disease recurrence or to exclude disease in those incorrectly identified as positive by a prior test or examination ('false-positive').

For each annual cohort of approximately 45,000 new cases of breast cancer, 20% (9000) will have developed metastatic disease and die within 5 years, requiring complex, demanding and costly treatment regimens. Taking a mean age of 70 years for primary breast cancer diagnosis, if 1% develop IBTR each year, and accounting for death from other causes, then over a 20-year period approximately 6358 patients will require treatment for this with 20% requiring further treatment for systemic disease.

Current service provision

Ipsilateral breast tumour recurrence and MCBC are detected by mammography, clinical breast examination and/or by the presence of symptoms noted by the patient. There are various recommendations in the UK for surveillance of patients with breast cancer ranging from 'no follow-up' to 6-monthly clinical examination (sometimes more frequently) and surveillance mammography (carried out at intervals ranging from 1- to 3-yearly). Follow-up is sometimes stratified by the likelihood of disease recurrence (defined as local and/or distant metastatic disease), based on prognostic factors taken from the patient's initial primary breast cancer. The majority of surveillance is carried out in secondary care (e.g. surgeons, oncologists, breast-care nurses), with patients being discharged to primary care after an interval which varies from 3 years to continued follow-up in secondary care. The uncertainty about best practice and current knowledge about variation in practice is further described below (see *Variation in services and/or uncertainty about best practice*).

Management of disease

Women with primary disease are usually treated using a combination of treatment modalities, including surgery, radiotherapy, chemotherapy, hormone therapy and biological therapy (trastuzumab), either alone or in a variety of combinations tailored to the patient and the type and stage of disease. However, most patients undergo surgery initially, which is either mastectomy or BCT, together with axillary surgery (sentinel lymph node biopsy, axillary sample or axillary clearance) and tailored adjuvant therapy afterwards. Patients with large or locally advanced breast cancer may receive either primary (neoadjuvant) chemotherapy or hormone

therapy prior to undergoing surgery. A small number of patients who are unfit for surgery but are hormone receptor positive may receive endocrine treatment and/or palliative radiotherapy as their sole treatment.

The management of locoregional recurrence following the treatment of primary breast cancer is variable in the UK, as there is an absence of RCTs to guide management decisions. Following breast conservation surgery it has been reported that, in those patients who experience locoregional recurrence, up to 20% may have distant metastases at the same time.[19,20] Furthermore, other studies have indicated that patients who experience a locoregional relapse have a reduced 5-year survival.[2,3] Where there is a recurrence in the chest wall after mastectomy, patients will frequently have systemic recurrence and therefore all patients presenting with recurrent breast cancer should be restaged [investigations may include combinations of haematological investigations, chest radiography, abdominal ultrasound, computerised tomography (CT) scan of chest and abdomen, isotope bone scan] prior to definitive management.[21]

A multidisciplinary approach is required for the management of patients with locoregional recurrence following treatment for primary breast cancer. For patients who have undergone breast conservation surgery, treatment is usually mastectomy (with axillary clearance if not already performed), together with consideration of further systemic therapy (chemotherapy, hormone therapy) to reduce the risk of subsequent metastatic relapse. In patients who have a local chest wall recurrence following mastectomy, local therapy (surgery if possible with radiotherapy afterwards or if surgery is not possible due to the extensive nature of the disease then radiotherapy alone) may be undertaken together with systemic therapy (chemotherapy, hormone therapy) given the high risk of subsequent metastatic relapse in this group of patients.

There are no RCTs on which to base the decision to offer systemic adjuvant therapies. In those patients without detectable systemic metastases, factors taken into account are as for the use of adjuvant therapy, for example tumour size, tumour grade, lymph node status, lymphovascular invasion, hormone receptor and human epidermal growth factor receptor 2 (HER2) status and the time interval from the treatment of the patient's original primary breast cancer.

Variation in services and/or uncertainty about best practice

There is considerable debate about the optimal organisation of a surveillance service following treatment for primary breast cancer. The number of different guidelines produced by various professional groups and policy-makers reflects this.[21–25] Previous surveys of breast surgeons, oncologists[26] and NHS breast-screening units[27] indicate that there is wide variation in follow-up practice but, in general terms, surveillance includes regular clinical examination, up to 3–5 years, with annual mammography for up to 10 years, or in some units this is carried out indefinitely. The most recent National Institute for Health and Clinical Excellence (NICE) guidance recommends mammography annually for 5 years and then follow-up through the NHS Breast Screening Programme (NHSBSP).[24] There is concern over whether the 3-yearly interval is sufficient for the group under surveillance, and some believe a stratified approach based on risk of recurrence or contralateral disease is more appropriate. The American Society of Clinical Oncology[28] recommended that surveillance should include annual mammography but acknowledges that there is a lack of high-level evidence to support decisions about the frequency and timing of mammographic surveillance. These guidelines have usually been based on consensus approaches and literature reviews, and their key recommendations are shown in *Table 1*.

For women who have had treatment for breast cancer there is, however, general agreement that there is no survival advantage conferred by an intensive surveillance regimen (comprising chest

TABLE 1 Comparison of guidelines for the surveillance of women who have received treatment for primary breast cancer

Organisation publishing guidelines	Clinical follow-up	Mammography	Additional comments
ABS at BASO[21]	Continue follow-up while on active treatments; at least 5 years recommended	1–2 yearly for up to 10 years after the primary diagnosis	High-risk or active treatment then more frequent and with agreed local protocols
SIGN[22]	Pragmatic – indefinite	1–2 yearly	
NICE (Cancer Service)[25]	Up to 3 years' follow-up	No recommendation	
NICE (Early and Locally Advanced Breast Cancer)[24]	Follow-up to completion of adjuvant treatment then choose setting in which follow-up occurs	Yearly for 5 years then move to NHSBSP screening – more frequently than 3-yearly stratified by risk	
RCR[23]		1–2 yearly	

ABS, Association of Breast Surgery; BASO, British Association of Surgical Oncology; RCR, Royal College of Radiologists; SIGN, Scottish Intercollegiate Guidelines Network.

radiography, liver ultrasound, haematological investigations and isotope bone scans) compared with a simpler follow-up schedule of clinical examination and mammographic surveillance.[29]

Given the variation in recommendations, it would be surprising if there were no variation in practice. The results of a survey of practice conducted for this study are described in more detail in *Chapter 3*.

Current and anticipated costs

As reported above, there are follow-up regimens for women following treatment of primary breast cancer. Illustrative annual costs of alternative surveillance regimens are presented in *Table 2*. The calculation of these costs is reported in detail in *Chapter 7*.

Description of technology

Surveillance mammography

Mammography has been in use for > 30 years and is the standard imaging technique for detection of breast cancer.[30] In women previously treated for breast cancer, surveillance mammography is useful for early detection of tumour recurrence or for confirming the absence of recurrent cancer. While tumour recurrence may display similar mammographic features to the previous primary breast cancer,[31] interpretation of the surveillance mammogram is hindered by changes in the breast caused by postoperative scarring and changes to breast density caused by primary treatment modalities. For example, following surgery and/or radiotherapy, detectable abnormalities on mammography include haematoma, scar formation, fat necrosis, skin thickening, increased soft tissue density in the ipsilateral breast and microcalcifications, all of which can be misinterpreted as malignancy. Therefore, surveillance mammography after the treatment for breast cancer is associated with the possibility of false-positive results causing further unnecessary investigations (invasive and non-invasive) and reduction in sensitivity for the detection of IBTR. There may also be an effect on MCBC detection with a lack of a comparator side.

Although published figures vary, it has been estimated that approximately 50% of IBTRs will be detected by mammography, with the remainder being detected by clinical examination.[31–33]

TABLE 2 Illustrative costs of alternative surveillance regimens

	Mammographic surveillance yearly for 10 years	Mammographic and clinical follow-up yearly for 10 years	Mammographic surveillance every 2 years for 10 years	Mammographic and clinical follow-up every 2 years for 10 years
Cost per woman per screen (£)	55.45	141.45	55.45	141.45
Cost for first episode of surveillance for an initial cohort of 10,000 women (£)	552,204	1,408,643	544,259	1,388,376
Cost over 10 years[a] (£)	5,147,650	13,131,382	2,552,363	6,510,943

a   Assuming that mean age of cohort is 57 years, women face the same risk of death as the general population and that they leave this follow-up regimen once cancer is detected.

Patients who have had a mastectomy or those who have undergone breast reconstruction following mastectomy do not have mammographic surveillance of that side. Clinical examination alone is the standard method of follow-up to detect IBTR, although mammography is undertaken of the remaining breast. Patients who have undergone mastectomy may find it easier to detect IBTR clinically than those who have undergone breast conservation surgery or reconstruction. Approximately 10% of breast cancers that can be palpated on clinical examination are not clearly visible on mammography and require the use of additional imaging techniques. Recurrent breast cancers detected by mammography are generally smaller and less aggressive than those found on clinical examination.[31,32] It is presumed, therefore, that mammography, combined with clinical examination, allows the earliest possible diagnosis of IBTR and also allows surveillance of the contralateral breast for the detection of MCBC. Whether such surveillance regimens reduce mortality remains unclear at present.

Mammography involves low-dose X-ray imaging of the breast to create detailed soft tissue, high-contrast, high-resolution images, which are recorded on photographic film. Mammograms are usually produced by a radiographer and interpreted by a radiologist who is trained in breast imaging. Recent developments have led to an increasing use of solid-state detectors rather than X-ray film, termed *digital mammography* or *full-field digital mammography* (FFDM). These convert X-rays into electrical signals. The images produced are displayed on a computer screen but can be printed onto radiographic film that is similar to conventional mammograms. It is possible to manipulate digital images on-screen to enhance visibility of certain areas. Digital mammography is quicker to produce than film mammography, uses lower doses of radiation and digital images require less physical storage space than traditional films. Digital mammography systems are, however, one to four times more costly than film mammography systems.[34] In the screening population, digital mammography has improved performance over film mammography in younger women and in women with dense breasts. Overall, however, the diagnostic accuracy of digital mammography is not significantly greater than that of film mammography.[35]

Other relevant new interventions
Imaging tests
Ultrasound
Breast ultrasound is an imaging technique for diagnosing breast cancer. A hand-held transducer produces high-frequency sound waves, which pass through the breast and reflect back or echo from various tissue surfaces to form an image of the internal structures. It is not an invasive technique and does not involve radiation. The transducer is linked to a computer so that images

can be viewed on a monitor screen. A radiologist or radiographer is responsible for interpreting the ultrasound images generated.

Breast ultrasound has been reported as having a lower sensitivity for detecting breast cancer than mammography.[36] When biopsies were indicated on the basis of the results of either mammography or ultrasound the positive predictive value was lower for ultrasonography than for mammography.[34] The use of ultrasound in routine practice is therefore mainly as an adjunct to mammography as a problem-solving tool to investigate an area in the breast which has been designated as 'suspicious' by mammography. Here, ultrasound acts as an additional diagnostic tool in determining whether a lesion identified on mammography or clinical examination requires further invasive investigation, for example in distinguishing between a fluid-filled cyst and a solid mass. Breast ultrasound is also particularly useful in evaluating women whose mammograms are difficult to interpret due to the density of their breasts.[37–39] Ultrasound is not used as a surveillance technique due to the low sensitivity of detection of breast cancer but can be helpful after mammography in order to differentiate scar tissue from IBTR or MCBC. It can also be used to undertake an ultrasound-guided biopsy of a suspicious area found on mammography. Ultrasound is a low-cost technique and, unlike mammography, does not involve any harm or discomfort to the patient. Test performance is operator dependent and time-consuming, however (approximately 30 minutes per ultrasound), and the results are less consistent than mammography.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) uses a powerful magnetic field and radio frequencies to produce detailed images of the breast. Breast imaging is undertaken using dedicated breast coils and with the patient lying prone on the examination table. The body coil around the base of the magnet sends radio waves into the breast tissues. The breast coils receive radio waves recording signals from the breast tissue. A computer then processes the signals and generates a series of images, each of which shows a thin slice of the breast, which can be viewed in different planes. An intravenous contrast agent is required to highlight breast cancers within the glandular tissue. The examination is carried out in the second week of the menstrual cycle to reduce background tissue enhancement.

Magnetic resonance imaging is used in women who are at high risk of developing breast cancer as a result of their family history; in distinguishing between scar tissue and recurrent tumour; in women for whom ultrasound and mammography findings are discordant; and in patients with lobular cancer and/or where there is suspected multifocal disease and a higher risk of MCBC. MRI has greater sensitivity than mammography or ultrasound, which makes it a particularly useful imaging modality for detecting small tumours and in women with dense breast tissue. Specificity, however, has been reported as being as low as 37%, as MRI is poor at distinguishing between cancer and benign breast disease.[34] MRI is not used as a primary surveillance tool at present.

The magnetic field used in MRI is not harmful, although internal medical devices that contain metal may malfunction or cause problems during an MRI examination. Some women may find the procedure uncomfortable and claustrophobic. There is also a small risk of mild allergic reaction if contrast material is injected. MRI investigations carry a greater financial cost (the *NHS Reference Costs*[40] report a mean cost of £232) than mammography (a mean cost of £45 for the mammogram alone has been estimated from Breast Screening Programme data) or ultrasound (the *NHS Reference Costs*[40] report a mean cost of £56). MRI is also more time consuming to perform (30–40 minutes) than mammography and is not as readily available, making it impractical to perform as part of the outpatient breast clinic.

Physical examination tests
Specialist-led clinical examination

Up to 10% of breast cancers are not detected by mammography but can be felt during a clinical breast examination. The clinical examination involves taking a history together with performing a physical examination (visual and palpation) of the breast(s) and lymph-draining areas (axillae, supraclavicular regions) and sometimes abdominal examination. It also provides an opportunity for monitoring treatment side effects (with appropriate therapy given as required) and its outcomes, changing adjuvant therapies, and providing psychological reassurance and treatment, if necessary, for the patient. This is conducted by a trained clinician and/or a nurse practitioner, and may be performed by other appropriately trained health-care professionals. If there are causes for concern then additional investigations can be undertaken, for example mammography, ultrasound or MRI. There is broad agreement for frequent clinical examination, usually at 6-monthly intervals initially and then annually for up to 3–5 years.[21,22,25]

Unstructured primary care follow-up (including primary care follow-up and self-examination)

Primary care follow-up Clinical follow-up of breast cancer patients is routinely coordinated and conducted in the secondary care outpatient hospital setting. Patients, however, may detect IBTR or MCBC themselves during the interval between clinic visits. There have been suggestions that follow-up could be transferred to the primary care setting with the general practitioner (GP) performing a similar role to the specialist clinician during the clinical examination.[29,41] If a GP detects a possible IBTR or MCBC, they should refer the patient back to the secondary care breast unit for further investigation.[21,24] Primary care follow-up also encompasses the role of the GP in assessment and referral of patients presenting in primary care with self-reported symptoms. These patients may be under secondary care supervision and/or may not have been taking part in any follow-up regimen for a variety of reasons. This latter group of women is classified as undergoing unstructured primary care follow-up, as they commonly self present with symptoms in the primary care setting.[41]

Self-examination The breast self-examination is a physical examination performed by the patient to detect any changes in the breast. Special training is given to the patient in palpation techniques and to promote breast self-awareness. Training teaches women how to identify new lumps in the breast or the axilla that may be potentially malignant, and to identify any changes, such as skin rash or nipple discharge, on examining the breast surface. Patients are also taught to recognise additional symptoms, such as bone, chest or abdominal pain, difficulty breathing and persistent coughs or headaches, that may be indicative of recurrent breast cancer. It is recommended that patients should perform a self-examination every month in addition to scheduled imaging and clinical examinations.[42]

Reference standard test

Histopathological examination is the commonly agreed reference standard for diagnosing IBTR or MCBC, based on tissue obtained from either a biopsy or cytological examination of a fine-needle aspirate. Histopathological examination of tissue is usually undertaken where there is a suspicion of malignancy on a prior surveillance test. In contrast, there is no reference standard for ascertaining the true-negative and false-negative measures of a surveillance test for IBTR or MCBC, although this is usually ascertained by a negative result or a positive test result at subsequent testing after a period of follow-up has elapsed (e.g. 1 year – mammography interval, 2–3 years – MRI interval, etc.). A pragmatic reference standard is therefore the diagnosis of IBTR or MCBC up to 3 years after a surveillance test has been carried out.

Identification of important subgroups of patients

It is known that certain groups of patients are at increased risk of IBTR. Those patients tend to be under 50 years of age at the time of diagnosis of their first breast cancer, have tumours classified histologically as being grade 3 cancers, have larger tumours, lymph node involvement and lymphovascular invasion (*Table 3* gives an estimate of importance of these factors in IBTR). Pathologists in the UK report this information routinely and much of these data are held by the cancer registries. We focused on these risk factors as it is possible to stratify patients according to these variables and also give some indication on the hazard ratio (HR) of developing IBTR or MCBC when taking these factors into account. These variables have been used to estimate prognosis, as with the Nottingham Prognostic Index, for example, which is based on tumour size, grade and lymph node status. Adjuvant! Online also uses similar criteria to calculate the benefits of different types of treatment for each particular patient.

TABLE 3 Factors associated with ipsilateral breast tumour recurrence[8]

Characteristics associated with primary tumour	10-year LR rate (%)	95% CI
Age at diagnosis (years)		
≤ 35	35	17 to 53
36–40	9	2 to 17
41–50	9	7 to 13
51–60	11	7 to 16
> 60	7	4 to 11
Tumour size (pathological) (cm)		
< 1.0	4	0 to 8
1.2–2.0	13	9 to 16
≥ 2.1	11	7 to 15
Nodal status (pathological)		
Negative	10	7 to 13
Positive	11	7 to 15
Histological type		
Infiltrating ductal	9	7 to 12
Infiltrating ductal with EIC	21	11 to 32
Infiltrating lobular	10	2 to 18
Histological grade		
Low/intermediate	7	5 to 10
High	15	10 to 19
Vascular invasion		
No	8	6 to 11
Yes	15	10 to 20

CI, confidence interval; EIC, extensive intraductal component; LR, local recurrence.

Chapter 2

Definition of the decision problem

Decision problem

There is considerable debate about the role and optimal organisation of follow-up of patients after treatment for primary breast cancer. The number of differing guidelines that have been produced by various professional groups and policy-makers reflects this.[21–23,25] There is broad agreement that surveillance should include frequent clinical examination, initially up to 3–5 years, with mammography starting 6 months after treatment, and then 1- to 2-yearly, for up to 10 years or indefinitely. The American Society of Clinical Oncology[28] recommended in 2006 that surveillance should include annual mammography, although acknowledging that there is a lack of high level evidence to support decisions about the frequency and timing of mammographic surveillance.

Seven reviews,[4,29,41,43–48] of varying methodological quality, have summarised the evidence of the effectiveness of differing surveillance regimens after treatment for breast cancer.

Summary of existing systematic reviews

Lu[5] recently conducted a systematic review to determine the impact of early detection of isolated locoregional and contralateral recurrence on survival. Thirteen studies considered routine follow-up (regular mammography and physical examination) or intensive follow-up (with the inclusion of routine additional tests) aimed at early detection of recurrence. The authors defined early detection as detection by mammography instead of physical examination or in asymptomatic patients, as opposed to those presenting with symptoms or detected via physical examination either by clinician or by the patient. The authors reported better overall survival for recurrences detected by mammography or in asymptomatic patients, with an absolute reduction in mortality of 17–28% if all breast cancer recurrences are detected early. The authors had insufficient data to study the contribution of differing frequency of mammography (e.g. yearly mammography compared with 6-monthly mammography) or to analyse the effect of prognostic factors such as age, tumour stage and surgical treatment. Rojas and colleagues[29] focused on the effectiveness of different surveillance policies for the detection of distant metastatic disease and concluded that follow-up programmes of regular physical examination and yearly mammography alone are as effective as more intensive approaches involving laboratory and radiological tests in terms of timeliness of detection of tumour recurrences, overall survival and quality of life. In addition, follow-up of patients performed by a trained general primary care practitioner is comparable to that of hospital-based secondary care specialists in terms of detection of tumour recurrence and quality of life. Collins and colleagues[44] reported that patient survival and quality of life were not affected by intensity of follow-up or location of care, although the authors note that data were not sufficiently homogeneous to integrate statistically. Montgomery and colleagues[46] systematically reviewed RCT evidence for alternative follow-up methods and concluded that the trials reviewed were not adequately powered to establish the safety of reducing or replacing hospital clinic visits.

Only Grunfeld and colleagues,[47] Montgomery and colleagues[46] and Barnsley and colleagues[43] specifically considered the role of mammography in surveillance, and Barnsley and colleagues[43] focused solely on surveillance mammography of the reconstructed breast, concluding that

certain local recurrences are detectable by surveillance mammography but that there is a paucity of evidence.

De Bock and colleagues[45] conducted a review of 18 uncontrolled, prospective and retrospective non-randomised studies of the effectiveness of routine follow-up visits and tests. The proportion of isolated locoregional recurrences diagnosed during routine visits or routine tests in asymptomatic patients was compared with the proportion of isolated locoregional recurrences in symptomatic patients. The authors were unable to assess whether recurrences, as defined by the study authors, were detected by physical examination or other tests, including mammography, or whether the detection of asymptomatic isolated recurrences had any influence on the potential for cure or quality of life of the patients.

Montgomery and colleagues,[4] in a meta-analysis of 12 studies (11 non-randomised cohorts and one randomised trial), aimed to determine the relevant contributions of clinical examination, patient self-examination and mammography to the detection of potentially treatable locoregional recurrence and contralateral primary cancers. It was reported that 30–40% of treatable recurrences, as defined by the study authors, were detected by the patients self-examining. Prior to 2000, 15% of relapses were mammographically detected compared with 46% detected by routine clinical examination. Post 2000, 40% were mammographically detected and 15% were detected through routine clinical examination. Patients with ipsilateral recurrence detected by clinical examination appeared to do less well in terms of survival than those detected by self-examination or mammography. The authors concluded that there was no evidence that clinical examination confers a survival advantage compared with other methods of detection and thus the need for clinical follow-up in detection of relapse is uncertain. The authors suggest that the temporal trend for increased detection by mammography is due to technical improvements in mammography and better quality assurance. Houssami and colleagues[48] recently reported a similar trend for mammographic detection, although they propose that this effect is largely due to increased uptake of surveillance mammography by women rather than increased sensitivity of mammography.

Grunfeld and colleagues[47] systematic review to define the effect of routine surveillance mammograms in detecting ipsilateral and contralateral cancer included 15 observational studies (published 1980–99). The 10 studies of ipsilateral recurrence showed that mammography detected the recurrence in between one-quarter and one-half of the women (range 8–50%), with the remainder being found by the women themselves between follow-up or by a hospital practitioner during clinical examination. The majority of studies did not report outcomes. Where this was reported, the method of detection of ipsilateral tumour did not appear to influence survival, except in the study conducted by Voogd.[49] Here it was reported that patients had a better 5-year survival if their tumour recurrence was detected mammographically. The nine studies of MCBC showed similar variation of detection methods. However, only one study reported outcome and this showed there was no difference in survival when comparing mammographic detection of the tumour with other methods.[33] The authors did not conduct a meta-analysis and concluded that further research is needed to better define the optimum surveillance mammography regimen following breast cancer treatment.

Overall, from these reviews the optimal frequency and duration of surveillance mammography is not clear. Furthermore, more recent information is required on whether there is new evidence concerning the effectiveness of surveillance mammography. This is now extremely important because of the development and use of new and increasingly effective treatments for patients with breast cancer since 1990. These may offer women an improvement in survival if there is an early detection of either IBTR and/or MCBC. A further limitation of all these reviews is that they did not consider the costs and cost-effectiveness of surveillance mammography compared with

other follow-up regimens despite there being methods for incorporating economic evidence into systematic reviews.[50] This is important because the evidence to date has not been systematically reviewed to assess whether or not surveillance mammography is cost-effective in the follow-up of patients with breast cancer. As health-care resources are limited, they have to be used effectively for the benefit of society. Using limited resources to provide surveillance mammography will mean that we cannot use those resources to provide some other form of potentially beneficial care. For surveillance mammography to be considered efficient the benefits that it provides must be greater than the benefits we could have obtained from providing other care.

Relevance of existing data to the decision problem

The introduction of the NHSBSP in the UK in 1988, coupled with advances in the treatment of primary breast cancer around 1990, has led to improvements in overall survival, with the 5-year relative survival rate now 82% in England and Wales.[1] Although long-term follow-up would be the most useful to inform the decision problem, technological developments in all aspects of diagnosis, treatment and follow-up of women make those women with the longest follow-up data the less relevant and their outcomes less generalisable to current practice. Therefore, in consultation with expert members of our Advisory Group (see *Appendix 1* for details of Advisory Group members) we decided to narrow our population of interest to consider data only for women treated for breast cancer from 1990 onwards. In addition, we decided not to include information from 1990 onwards relating to the Breast Screening Programme. This is because the screening population differs greatly to women who have been diagnosed and treated for breast cancer due to changes in breast density following treatment for primary breast cancer. We therefore felt that it would be inappropriate to use data from breast-screening studies of test performance in the systematic reviews (*Chapters 4* and *5*) to make assumptions regarding test performance for surveillance of the contralateral breast. We used parameter estimates for MRI test performance in the screening population in the economic evaluation in *Chapter 7* of this report; however, it was felt that these would provide an indication of the relative value of a more costly but more effective test.

Key issues

The key issues to be addressed are:

- Can surveillance mammography improve overall survival for women treated for primary breast cancer?
- Does surveillance mammography improve detection of IBTR and MCBC?
- What is the incremental cost-effectiveness of surveillance mammography?

Current care pathway

There are a number of different surveillance mammography regimens in place in the UK for women following the treatment of primary breast cancer. In this section, we describe current pathways of care for women who are diagnosed, treated and followed up for breast cancer. In *Chapter 3* we describe the potential alternative care pathways that we will attempt to consider and how we derived them.

However, when evaluating different surveillance regimens it is important to understand the sequence of care that a woman might receive after treatment for a primary breast cancer. Consideration can then turn to how different surveillance regimens may alter the care that a woman may receive over time.

Care pathways for current practice

We developed a care pathway for Aberdeen via discussions with experts in Aberdeen (*Figures 2–4*). This care pathway starts with initial presentation and describes the sequence of
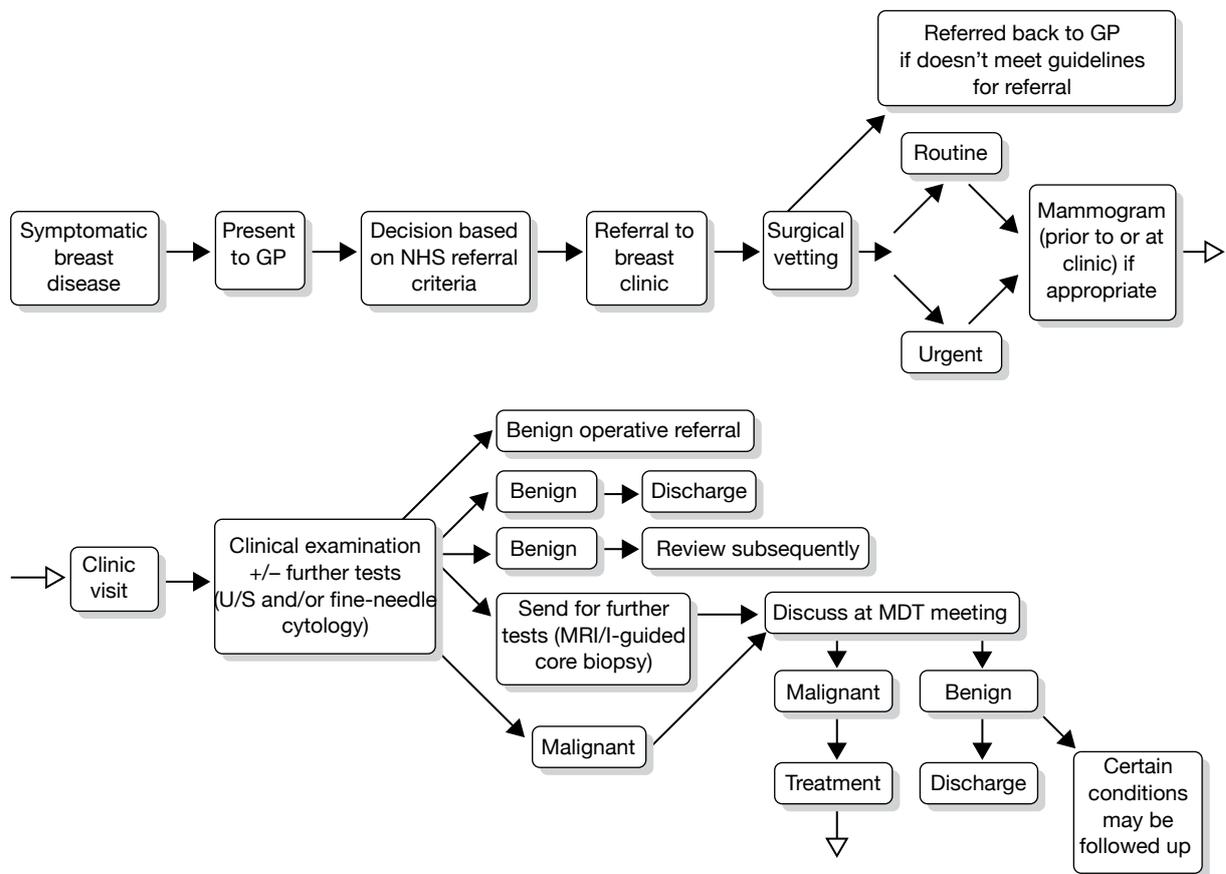
FIGURE 2 Current care pathway: Aberdeen: diagnosis of breast cancer – symptomatic presentation. I-guided core biopsy, image-guided core biopsy; MDT, multidisciplinary team; U/S, ultrasound.

events from diagnosis, through treatment and eventual longer-term follow-up. It is useful to consider the whole sequence of events, but of central importance to this project is how different surveillance regimens will potentially alter this care pathway.

Development of alternative surveillance regimens

Taking the care pathways above as a basis, we used the data reported in *Chapter 3* to identify potentially relevant pathways for alternative surveillance regimens. We also considered whether or not there are any clinically attractive follow-up regimens that might not be used in practice but that we might consider useful to estimate their effectiveness, cost-effectiveness and feasibility in our subsequent modelling exercise. This consideration was partly informed by our discussions at the last Advisory Group Meeting, the literature and the results of our survey reported in *Chapter 3*.

When considering what surveillance regimens might be relevant, answers to the following questions were sought.

For mammographic surveillance:

- For which women is the issue of mammographic surveillance relevant?
- What mammography surveillance should be used?
- Does it vary between women and if so why would it vary?
- How often is it performed?
- Where does it take place?
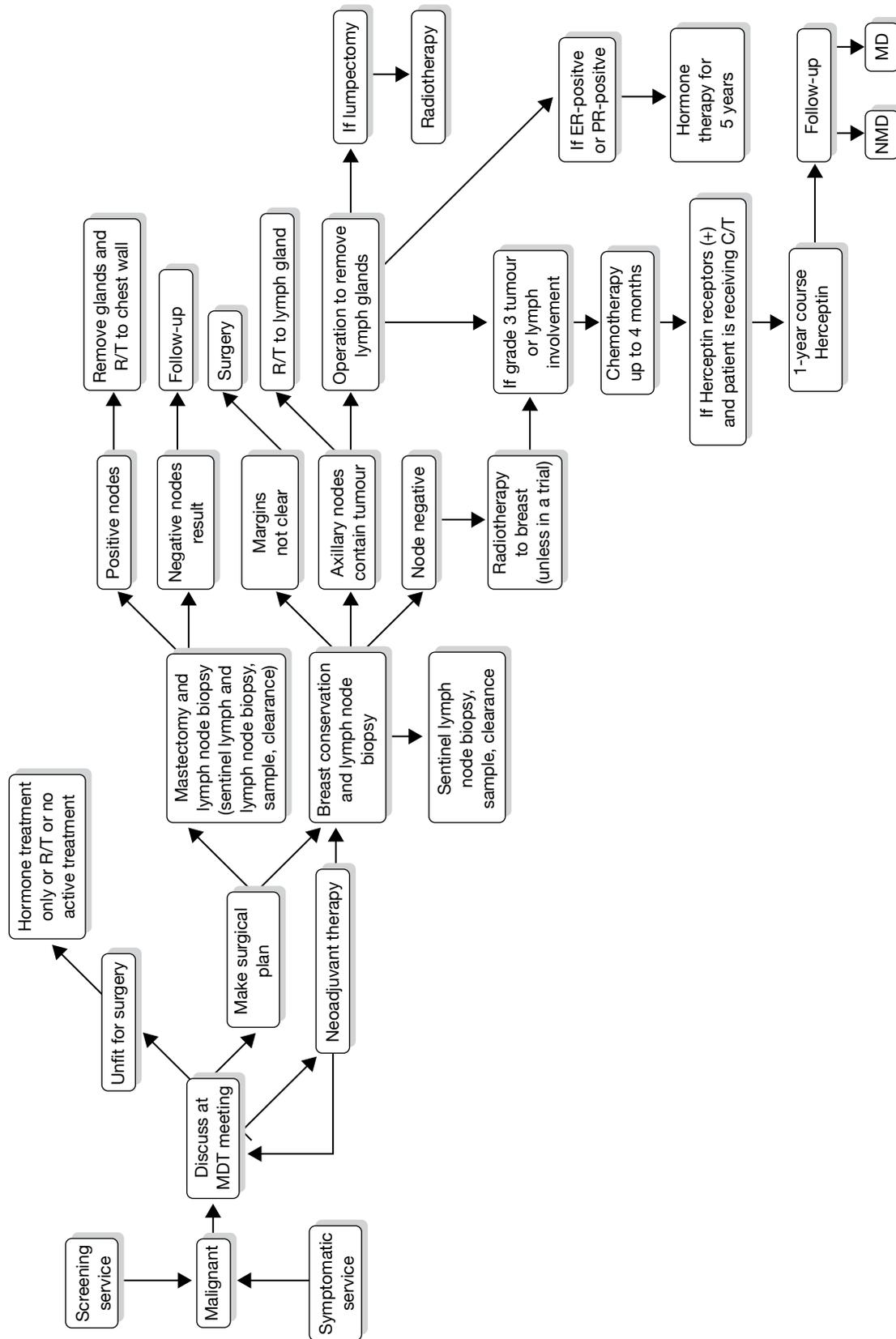
FIGURE 3 Current care pathway: Aberdeen – clinical management of a woman presenting with a malignancy. CT, chemotherapy; ER, oestrogen receptor; MD, metastatic disease; MDT, multidisciplinary team; NMD, non-metastatic disease; PR, progesterone receptor; R/T, radiotherapy.
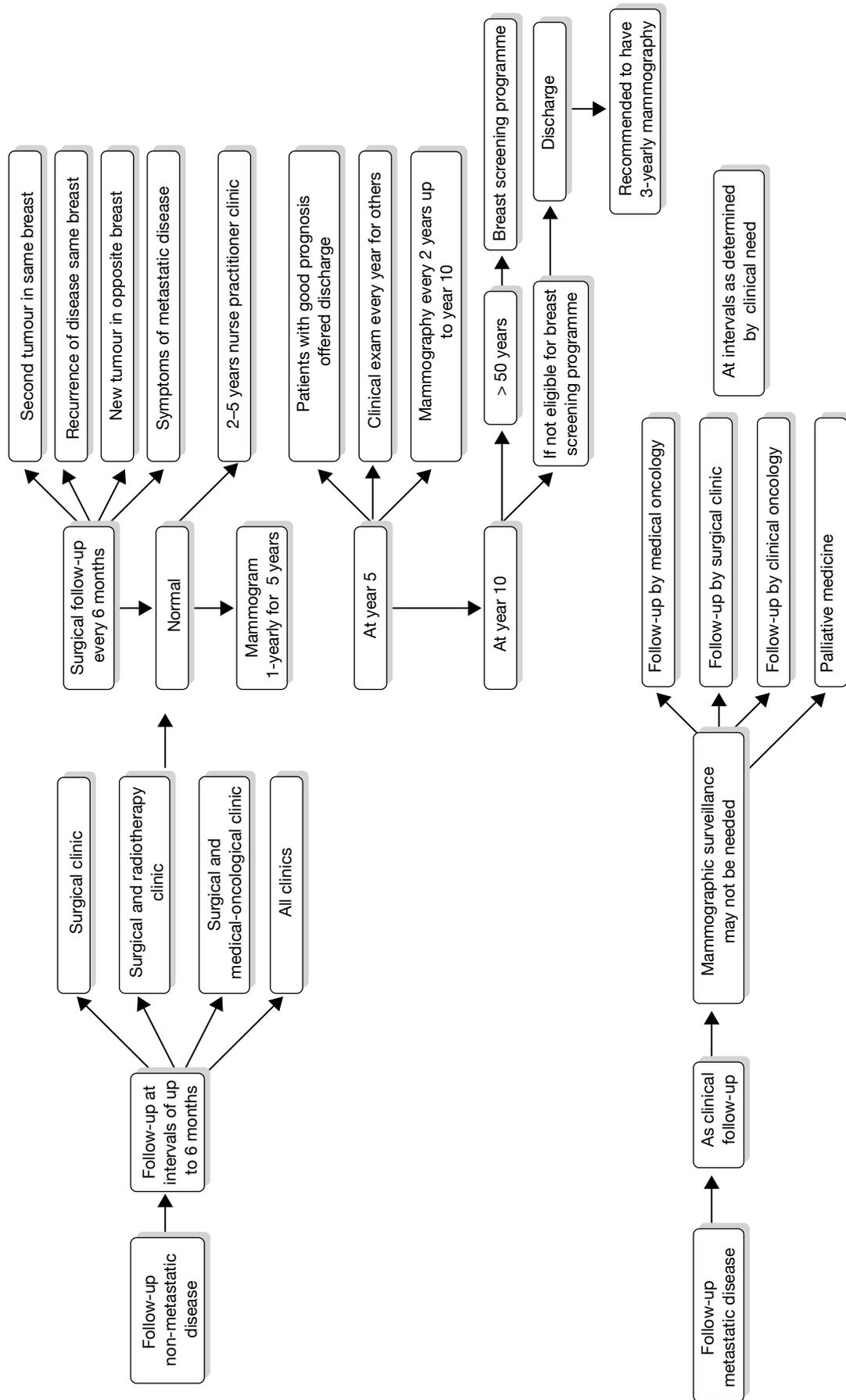
FIGURE 4 Current care pathway: Aberdeen: follow-up of non-metastatic and metastatic disease.

For clinical follow-up:

■   What clinical follow-up is used?
■   Does it vary between women and if so why?
■   Where does it take place?
■   How often?

For unstructured primary care follow-up:

■   How might a diagnosis be made?
■   At what point would these women enter the care pathway described in *Figures 2–4*?

More specifically, what factors might influence the choices made about mammographic surveillance and clinical follow-up?

Other factors to consider:

■   age
■   risk factors
■   type of primary disease
■   type of treatment.

We describe the care pathways developed from this process in *Chapter 3*. We then used the care pathways to structure data collection in the remainder of the project and to help to define the comparators for the economic evaluation. The structure of the model, which is detailed in *Chapter 7*, was based upon the current care pathway described above. The structure of the economic model was defined to directly address the aim of the review set out below.

Aim of the review

To examine the clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer in the UK in primary and secondary care settings.

The aim is addressed through:

1. A survey of UK breast surgeons and radiologists to identify current practice and estimate resource consequences of the varying regimens.
2. Two discrete systematic reviews to determine the clinical effectiveness of differing surveillance mammography regimens after treatment for breast cancer on patient health outcomes and the diagnostic accuracy of surveillance mammography in the detection of IBTR and MCBC.
3. Statistical analysis of individual patient data and and economic modelling using the systematic review results, existing data sets and focused searches for specific data analysis to determine the effectiveness and cost–utility of differing surveillance regimens.

The specific objectives are to:

1. identify feasible management strategies for surveillance and follow-up of women after treatment for breast cancer in a UK context

2. determine the effectiveness of differing surveillance and follow-up regimens after treatment for breast cancer
3. estimate the costs of differing regimens for surveillance and follow-up regimens after treatment for breast cancer
4. estimate the cost-effectiveness of differing regimens for surveillance and follow-up regimens after treatment for breast cancer
5. identify future research needs.

Structure of the remainder of the report

The remainder of the report is structured as follows: *Chapter 3* describes a survey of current practice and feasible management strategies for surveillance in the UK; *Chapter 4* assesses the clinical effectiveness of surveillance mammography, *Chapter 5* assesses test performance of surveillance mammography compared with alternative diagnostic tests and combinations of diagnostic tests. *Chapter 6* describes the analysis of individual patient data (Breast Cancer Registry database) and *Chapter 7* assesses the cost-effectiveness of surveillance mammography. *Chapter 8* is a discussion of the findings and *Chapter 9* presents the review's conclusions, including implications for NHS service provision and for future research priorities.

Chapter 3

Identifying feasible UK management strategies for surveillance mammography and follow-up of women after treatment for primary breast cancer

Overview

In the UK, there is considerable debate about the role and optimal organisation of a surveillance service following breast cancer treatment. The number of different guidelines produced by various professional groups and policy-makers reflects this. The guidelines include those of the British Association of Surgical Oncology (BASO) 2009,[21] the NICE *Guidance on Cancer Services* 2002,[25] the NICE *Early and Locally Advanced Breast Cancer: Full Guideline* (CG80) 2009,[24] the Royal College of Radiologists (RCR) Breast Group 2003,[23] and the Scottish Intercollegiate Guidelines Network (SIGN) 2005.[22] Typically, consensus approaches and literature reviews are the basis for these guidelines. We show the variations in key recommendations in *Table 1* (see *Chapter 1*).

Donnelly and colleagues' survey in 2007[26] of 256 specialists registered to Cancer Trials Units suggested that the majority (84%) adhered to locally developed protocols for surveillance, and annual mammography was the most common surveillance interval for both invasive and non-invasive disease. Maxwell and colleagues' survey of breast-screening units taking part in the Sloane project[27] concluded that there was wide variation in follow-up practice after surgery (breast conservation or mastectomy) for non-invasive breast cancer. The most common frequency of clinical follow-up was annual for up to 5 years and, for surveillance mammography, annual up to 10 years after breast conservation, and annual or biennial to 10 years after mastectomy.

The optimal frequency and duration for conducting surveillance mammography is unclear, thus leading to variation in follow-up protocols for breast cancer throughout the UK.

Aim

To describe the variations in current mammographic surveillance and follow-up practice in the UK, in order to inform the development of the care pathways for the economic evaluation.

We addressed this aim via a survey of breast surgeons and radiologists (see *Methods for the survey* and *Results of the survey*) and consultation with our expert project Advisory Group.

Methods for the survey

Objectives

- To identify current UK surveillance mammography regimens.
- To inform the feasible alternative surveillance regimens (care pathways) for:
  - populating the economic model
  - informing the systematic reviews
  - providing context for the individual patient data analysis.
- To inform the choice of comparator surveillance regimens (inclusive or not of mammography) for the systematic review components of the wider project.

Population and sample

Our population was all health-care professionals providing surveillance of women following treatment for primary breast cancer. We chose our sample from this population to reflect those most likely to be currently involved with organising and/or undertaking surveillance mammography and to try to ensure UK-wide information. We sampled from the Association of Breast Surgery (ABS) at the BASO and the RCR Breast Group. Both the ABS and RCR Breast Group (to the best of their knowledge) held current and complete e-mail contacts for their members and these lists formed our sample. We sampled all full members (496) and associate members (73) of the ABS, and ordinary members (447 radiologists) and associate members (32 breast physicians) of the RCR Breast Group. We excluded the retired and overseas members of both organisations.

Data collection, management and analysis

Questionnaire development

We developed a questionnaire for use in a web-based survey (*Appendix 2*). The development of the data items and questions were informed by recently published similar surveys[26,27] and with the expert advice of the project Advisory Group. We tested the questionnaire items with members of the project Advisory Group and subsequently piloted the questionnaire with the first 100 members on the ABS and RCR e-mail distribution lists.

Survey invitation and distribution

We invited the ABS and RCR Breast Group members to participate in the survey via an e-mail-based web link to the online questionnaire sent to them by the ABS and RCR Breast Group membership administrators. All responses to the survey were anonymous. The Health Services Research Unit (HSRU) (University of Aberdeen) Programming Team created a web-based version of the survey questionnaire (see *Appendix 2* for content details).

The ABS and RCR Breast Group membership administrators e-mailed the link to the questionnaire through a secure website using the e-mail distribution lists for each college. The website used for sending the questionnaire URL was password protected to prevent unauthorised access. Only persons with authorised login were able to access this website. Once logged on to this site, the administrators added the individual e-mail addresses into a text box for submission. An automated e-mail (see *Appendix 3* for content details) was then sent to all submitted e-mail addresses, containing text inviting potential participants to consider participating in the survey and the URL link to the survey questionnaire itself. The administrators were able to view only the e-mail addresses they submitted and were not able to view e-mail addresses entered by any other administrator.

Once potential participants received the e-mail they could then access the survey questionnaire by clicking the URL hyperlink contained in the e-mail. Participants could then complete and submit the questionnaire. Participants could view their own data only.

We could not target reminders to individuals who had not responded, as participants' responses were anonymous. One general reminder e-mail was sent via the ABS and the RCR Breast Group membership administrators to all potential participants after the initial mailing, asking those members who had not yet completed the survey to consider doing so (see *Appendix 4* for content details).

We tested the survey invitation and distribution with members of the project Advisory Group and subsequently piloted with the first 100 members on the ABS and RCR e-mail distribution lists.

Ethics and consent

We consulted members of the North of Scotland Research Ethics Service to consider whether the survey required review by a Research Ethics Committee (REC). They had access to the aims, objectives and the content of the questionnaire and concluded that as they viewed it as service evaluation it did not require REC review.

The text of the accompanying e-mail and the survey form itself informed potential participants that their responses were anonymous and the information would be held in strictest confidence.

The project team did not have access to the e-mail addresses of individual ABS or RCR Breast Group members, nor did the questionnaire contain individual personal details. Submitted survey data were stored within a secure database on a secure server within HSRU. All researchers who could have access to the data had signed and were required to adhere to a 'Protecting Information Policy' and were expected to adhere to the principles of Good Clinical Practice (GCP).

Data management

The website used for sending the survey invitation e-mails automatically generated unique, study identifiers (study ID) for each completion of the survey without identifying individual e-mail addresses. Submitted survey data were stored within a secure database on a secure server within HSRU. We cleaned survey data and recoded text fields as required.

Data analysis

We defined the response rate to the survey as the number of participants who responded divided by the numbers of potential participants on the ABS and RCR Breast Group e-mail distribution lists. We summarised the responses to the survey by type and frequency (%).

Results of the survey

We received responses from 17% (183/1048) of those surveyed (see *Appendix 5* for the number and percentage of respondents who completed each question). The majority of respondents (64%) named their specialty as surgery and 35% as radiology (*Table 4*). Fifty per cent of individuals practise in units that annually manage > 300 women with newly diagnosed breast cancer, with 26% practising in units managing between 200 and 300 women with breast cancer (*Table 4*). Respondents were based in 105 NHS trusts across the UK (see *Appendix 6* for the list

TABLE 4 Respondent specialty and unit size

Specialty	No. (%) of respondents	
	n = 183	Percentage of *n*
Surgery	117	63.9
Radiology	64	35.0
Other	2	1.1
No. of women with newly diagnosed breast cancer unit manages annually		
< 100	5	2.7
100–199	33	18.0
200–300	48	26.2
> 300	92	50.3

of NHS trusts) and one in full-time private practice. The number of respondents per trust was just one for 60 trusts (57%); in 26 trusts (25%) there were two respondents and in 12 trusts (11%) there were three respondents; the maximum number of respondents per trust was six, with only seven trusts with four or more respondents per trust.

Initiation, frequency and duration of surveillance mammography

The large majority of respondents initiate surveillance mammography at 12 months post surgery for women who have had breast-conserving surgery (BCS) (87%) and for women who have had a mastectomy (79%) (*Table 5*).

Responses ranged from six to 24 months post surgery, with the next most frequent being 24 months (13%) post mastectomy.

Table 6 shows the respondents standard practice frequencies or intervals of surveillance mammography for women after BCS and after mastectomy. Annual surveillance mammography was the most commonly reported standard frequency of surveillance mammography for women after BCS or after mastectomy (72% and 53%, respectively), with biennial mammography the next most frequently reported (12% and 30%, respectively). The 'other' responses varied but can generally be described as showing a pattern of increasing mammography surveillance intervals with increasing time since surgery, for example surveillance mammography at 1, 2, 3, 5, 7 and 10 years.

Fourteen per cent (26/180) of respondents said that they varied their standard surveillance mammography practice (initiation of surveillance mammography post surgery or frequency of mammography) for women who had BCS. They varied their practice according to the survey-prompted criteria of in situ tumours (*n* = 14); size of tumour (*n* = 5); grade of tumour (*n* = 1); lymphovascular invasion (*n* = 4); age (*n* = 9); absence of radiotherapy (*n* = 3); combinations of these (*n* = 2); or other criteria (*n* = 10). Other criteria included 'close margins', comorbidities, family history and genes predisposing to breast cancer.

Similarly, 13% (23/180) varied their standard surveillance mammography practice (initiation of or frequency) for women who had a mastectomy, by factors such as age, cancer grade and size, comorbidities, family history, genes predisposing to breast cancer or 'high-risk' groups.

In addition, a further 16/183 (9%) commented in text within the questionnaire that they vary their standard initiation and frequency surveillance practices, trying to take into account factors

TABLE 5 Initiation of surveillance mammography

	After BCS		After mastectomy	
	Number and percentage of respondents			
No. of months post surgery	$n = 181$	Percentage of n	$n = 159$	Percentage of n
6	7	4	2	1
8	1	1	0	0
9	2	1	1	1
11	3	2	1	1
12	157	87	125	79
18	7	4	9	6
24	4	2	21	13

TABLE 6 Frequency of surveillance mammography

	After BCS		After mastectomy	
	Number and percentage of respondents			
Frequency of surveillance mammography	$n = 182$	Percentage of n	$n = 181$	Percentage of n
Annually	131	72	96	53
Every 18 months	11	6	16	9
Every 2 years	22	12	54	30
Every 3 years	0	0	5	3
Annually to 5 years then every 2 years	9	5	6	3
Other	9	5	4	2

such as age, density of breast tissue, comorbidities, family history, genes predisposing to breast cancer or 'high-risk' groups.

When asked about through which service they arrange their surveillance mammography, the majority responded [175/182 (96%)] that it is through their symptomatic breast service, although seven (4%) said through the NHSBSP.

The majority (75%, 136/182) indicated they discharge women from surveillance mammography and they do this most frequently 10 years after surgery (*Table 7*). The majority (82%, 148/180) do discharge from clinical follow-up and most frequently at 5 years (*Table 7*). Just over half (55%, 98/179) responded that they discharge women to the NHSBSP (*Table 8*) if eligible.

However, around 28% (47/167) of those who discharge from follow-up (clinical and/ or mammographic follow-up) commented that they vary the duration of surveillance mammography and this is influenced by the age of the women (24%), or by other factors including family history, genes predisposing to breast cancer, and tumour characteristics.

Combining our respondents' standard initiation, frequency and duration of surveillance mammography resulted in 54 differing surveillance regimens for women after BCS and 56 for women following mastectomy (*Appendices 7* and *8*, respectively). Fifty-one per cent (79/154) of respondents follow one of four surveillance regimens for women after BCS. The most commonly followed regimens are to initiate surveillance mammography at 12 months after surgery and conduct annual surveillance mammography with indefinite duration (12%, 19/154); discharge

TABLE 7 Duration of surveillance mammography: discharge from surveillance mammography and from clinical follow-up

	Discharge from:			
	Surveillance mammography		Clinical follow-up	
	Number and percentage of respondents			
Discharge				
	n = 182	Percentage of *n*	*n* = 180	Percentage of *n*
No	46	25	32	18
Yes	136	75	148	82
How many years post surgery				
	n = 121	Percentage of *n*	*n* = 130	Percentage of *n*
1	0	0	3	2
2	0	0	2	1
3	1	1	9	7
5	42	35	85	65
6	3	2	1	1
8	1	1	1	1
9	6	5	0	0
10	67	55	29	22
11	1	1	0	0

TABLE 8 Duration of surveillance mammography: discharge to NHSBSP

Discharge to NHSBSP	Number and percentage of respondents	
	n = 179	Percentage of *n*
No	81	45
Yes	98	55
At age (years)		
	n = 39	Percentage of *n*
50	26	67
70	3	8
75	1	2
Or years of follow-up		
	n = 39	Percentage of *n*
5	2	5
6	1	2
9	1	2
10	5	13

from both clinical and mammographic surveillance at 5 years (14%, 22/154) or 10 years (12%, 18/154) after surgery; or discharge from mammographic surveillance at 10 years and clinical follow-up at 5 years (13%, 20/154). Similarly, after mastectomy the most commonly followed regimens are to initiate surveillance mammography at 12 months after surgery and conduct annual surveillance mammography, with indefinite duration (7%, 10/136); or discharge from both clinical and mammographic surveillance at 5 years (10%, 13/136); or 10 years

(11%, 15/136) after surgery; or discharge from clinical follow-up at 5 years with continued mammographic surveillance until 10 years (8%, 11/136).

Ideal practice

Twenty-nine per cent (53/180) of respondents suggested that their ideal surveillance mammographic practice differs from their current practice and that this is influenced by the factors listed in *Box 1*.

The most common ideal frequency of surveillance mammography given was annually for women who had undergone BCS (80%, 85/106) or mastectomy (57%, 61/106) (*Table 9*). These ideal frequencies of surveillance did not differ from their current practice for the majority of respondents, for women after BCS (80%, 84/106) or for women after mastectomy (69%, 73/106). However, three respondents suggested that their ideal practice would be to arrange surveillance mammography through the screening units, as they are set up to manage the appointment and recall system.

Care pathway development

We used the results of our survey, other relevant surveys[26,27] and advice from the clinical experts involved in this study to identify alternative follow-up regimens. This work formed the basis for the care pathways, which, in turn, provided the basis of the economic model that is described in *Chapter 7*. The economic model aims to determine the effectiveness and cost–utility of differing surveillance regimens.

BOX 1 Factors that influence why ideal practice differs from current practice

Administration

Capacity

Cost or funding

Evidence to guide decisions

Infrastructure

Organisation and resources

Local and national policies and guidance

Patient and staff preconceptions

TABLE 9 Ideal frequency of surveillance mammography

Ideal frequency of surveillance mammography	After BCS		After mastectomy	
	Number and percentage of respondents			
	n = 106	Percentage of *n*	*n* = 106	Percentage of *n*
Annually	85	80	61	57
Every 18 months	5	5	18	17
Every 2 years	9	8	21	20
Every 3 years	0	0	0	0
Annually to 5 years, then every 2 years	0	0	0	0
Other	7	7	6	6

Development of alternative surveillance regimens

Taking the care pathways described in *Table 1* (see *Chapter 1*) and *Figures 1–3* (see *Chapter 2*) as a basis, we used the results of the surveys to identify if there were any clinically attractive follow-up regimens that might be used in practice or are currently not used in practice. This consideration was partly informed by our discussions during project Advisory Group Meetings (which were informed by the literature and the results of the survey described above).

When considering what surveillance regimens might be relevant, answers to the following questions were sought, which can be briefly summarised as: who would be under surveillance/follow-up; what technology would be used (e.g. mammography, clinical examination, etc.); where would the surveillance be performed; who would perform the surveillance; and what would be the frequency of surveillance/follow-up (the questions used are described in more detail in *Appendix 9*).

Surveillance regimens

Figure 5 describes the potential alternative care pathways developed from this process. For example, individuals can be followed up using surveillance mammography at different intervals, for example once yearly, every 18 months, every 24 months or every 36 months. Alternatively, individuals could present to a GP with a problem, i.e. discover a lump. Individuals who present to their GP with a lump would be given a clinical examination by the GP. Current practice in the economic model is assumed to be once-yearly mammograms.

The alternative surveillance regimens in the economic model vary by screening interval and/or screening technology. For example, alternative mammographic surveillance regimens to the standard regimen would be for mammography to take place at less or more frequent intervals, for example every 18 months or every 24 months. Although not explicitly noted, one important option to consider as an alternative would be surveillance mammography organised through the NHSBSP.

Alternative primary care regimens would be for an individual to attend a GP surgery and receive a clinical examination followed by a mammogram if there was a suspicious finding on the clinical examination. Other potential surveillance regimens include the use of alternative technologies, i.e. MRI or ultrasound in replacement of mammography. For all regimens other than GP opportunistic finding, individuals are invited to attend screening at different intervals, for example once yearly. An individual can either choose to attend or not attend the screening programme. Given that this is a higher-risk group (women who have previously had breast cancer), and, also for simplicity of modelling, we are assuming that all individuals who are invited for screening do attend. In the intervals in which screening does not occur, we assumed that individuals could still be diagnosed with breast cancer through their GP.

Following further discussion within the project Advisory Group, these options were further reduced to three regimens that we felt broadly represented the most relevant comparators. This decision was also informed by knowledge of the preliminary findings of the research reported in *Chapters 4–6*. These regimens were: mammographic surveillance with and without clinical follow-up organised either through secondary care or through the screening service (this option embraces regimens 1, 3 and 6 in *Figure 5*) and the identification of cancer following referral from primary care following the identification of a suspicious lump on self-examination (regimen 7).

	Setting		Technology		
1	Secondary care	→	Mammography		
2	Secondary care	→	Clinical exam		
3	Secondary care	→	Clinical exam	→	Mammography
4	Secondary care	→	Other technology		
5	Primary care	→	Clinical exam		
6	Screening service	→	Mammography		
7	Primary care	→	Unstructured		
8	Primary/secondary care	→	Questionnaire F/U		
9	Primary/secondary care	→	Telephone F/U		
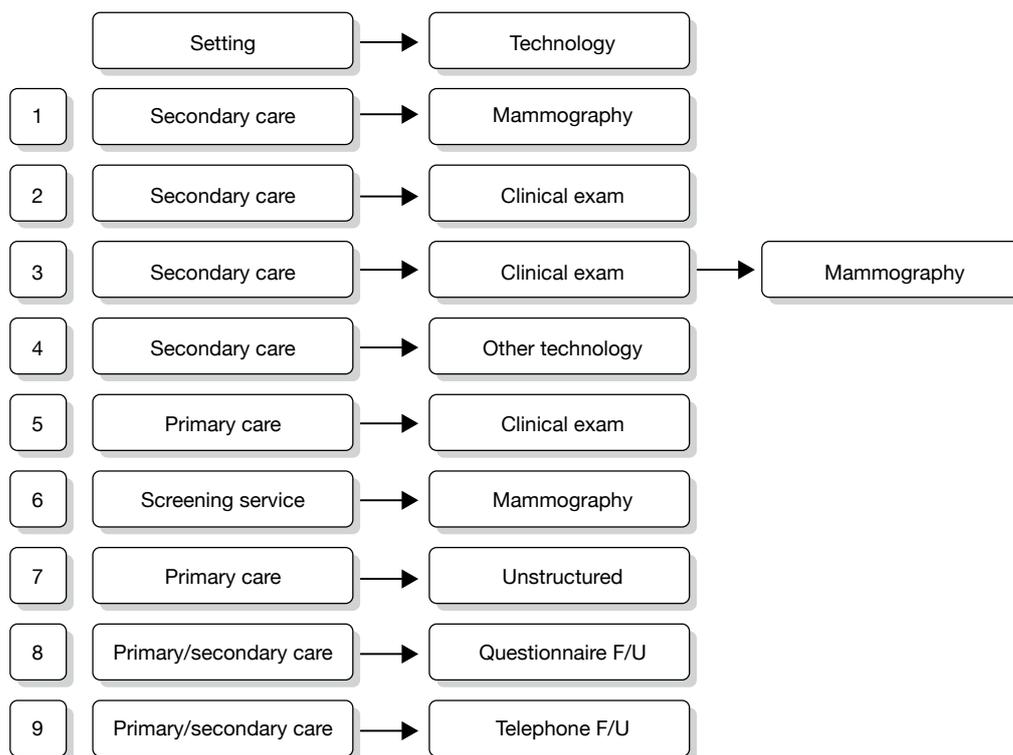
FIGURE 5 Potential alternative care pathways. F/U, follow-up.

Discussion

The findings of our survey suggest that although common patterns in surveillance mammography practice exist there is considerable variation in the way surveillance is organised.

The most commonly followed regimens for surveillance of women after BCS are to initiate surveillance mammography at 12 months after surgery and conduct annual surveillance mammography with indefinite duration, discharge from both clinical and mammographic surveillance at 5 or 10 years after surgery, or discharge from mammographic surveillance at 10 years and clinical follow-up at 5 years. Similarly, after mastectomy the most commonly followed regimens are to initiate surveillance mammography at 12 months after surgery and conduct annual surveillance mammography, with indefinite duration or discharge from both clinical and mammographic surveillance at 5 or 10 years after surgery or discharge from clinical follow-up at 5 years with continued mammographic surveillance until 10 years. However, respondents varied greatly in the combinations of start, frequency, duration and discharge from surveillance mammography.

Our findings reflect the varying guidance given by the various professional organisations with an interest in surveillance after breast cancer (see *Table 1, Chapter 1*) in combination with 'local circumstances' of the respondents, and are generally consistent with those of recent surveys addressing similar questions.[26,27]

Our response rate was not high in comparison with what might be expected for a postal questionnaire in medicine or in comparison with the recent surveys.[26,27] We discuss further the implications of this in *Chapter 8*.

The plethora of different ways of conducting surveillance mammography in practice mean that there are potentially a large number of care pathways that are worthy of further consideration. It would not be possible to consider the merits of each of these options especially when there are additional methods of follow-up that do not include mammography. Therefore, using the results of the survey and expert opinion provided by the project group, a relatively small number of follow-up methods were defined, which differed by the diagnostic technology used. It is possible, however, that this list excludes potentially important pathways.

Chapter 4

Systematic review of clinical effectiveness of surveillance mammography after treatment for primary breast cancer

Overview

As *Chapter 3* illustrated, although there is some similarity between surveillance regimens used in practice there is also considerable variation. It is unclear which of these alternative methods of organising a service represent the most effective and efficient regimen. Previous systematic reviews [4,29,43–47] have been unable to clarify the optimal frequency and duration of surveillance mammography.

We conducted a systematic review to determine the clinical effectiveness of differing surveillance mammography regimens after treatment for primary breast cancer in detecting IBTR and MCBC. The results of this review were used to inform the economic evaluation described later in this report (*Chapter 7*).

Methods

Inclusion and exclusion criteria
Types of study
Evaluations of any screening or follow-up regimens are prone to lead and length time bias, i.e. detecting tumours early in the course of disease without influencing survival (lead time bias) or detecting slower growing tumours that would not reduce length of life or underdetecting rapidly progressive tumours that have a poorer survival prognosis (length time bias). As RCTs are the optimal method of ameliorating for these biases, we included RCTs of differing surveillance mammography regimens and alternative breast cancer follow-up regimens in this evaluation, i.e. where women are randomly allocated to one surveillance regimen or another. In addition, we included non-randomised comparative studies of differing surveillance mammography regimens and alternative breast cancer follow-up regimens. We also included prospective and retrospective cohort studies of differing surveillance mammography regimens or alternative breast cancer follow-up regimens containing 100 or more participants and where participants were followed up for at least a median time of 5 years.

All studies were required to include participants with a diagnosis of primary breast cancer from 1990 or later. In consultation with expert members of our Advisory Group, we chose 1990 as the start date for our inclusion criteria to avoid the introduction of bias for overall survival outcomes. Improvements in overall survival around 1990 are attributable to the introduction of the NHSBSP in the UK, coupled with advances in the treatment of primary breast cancer and changes to the ways in which patients with breast cancer are managed. The 5-year relative survival rate is now 80% in England and Wales.[1]

Types of participants
Women previously treated for primary breast cancer without detectable metastatic disease at their initial presentation for treatment.

Types of interventions
Routine surveillance mammography for detecting IBTR and/or MCBC.

Comparator(s)
- No surveillance mammography.
- Differences in frequency of surveillance mammography regimens.
- Alternative follow-up regimens, for example, including, but not limited to, breast-care physician-led clinical examination.

Types of outcome measures
We included studies that reported any of the following outcomes:

- *Primary outcome* – overall survival. We defined overall survival as the amount of time that a woman remains free from all-cause mortality following primary treatment. We also considered mortality rates to optimise data collection of outcome measures relating to the effectiveness of a surveillance regimen.
- *Secondary outcomes* – IBTR and/or MCBC event rate. We considered event rates and time to detection of IBTR and/or MCBC. We did not include tumour recurrences outside of the breast, for example regional (axillary) recurrence, or distant metastatic disease, as we would not expect surveillance mammography to detect these types of disease recurrence.
- *Quality of life* – We considered any measure of health-related quality of life attributable to surveillance mammography or other follow-up regimen.
- *Harms of mammography (adverse events)* – Undergoing mammography entails exposure to radiation, which carries a small risk of developing cancer. Mammography can also be an uncomfortable procedure that can cause pain in some women. Following mammography, further investigations may be required, which subsequently turn out to be normal.
- *Uptake of mammography* – We considered data relating to numbers of women attending for planned surveillance mammography.
- *Economic data* – Reporting of any data on costs to the NHS and patients including resource use for the actual interventions and resource use consequent to implementation of that intervention, which may occur up to the end of the woman's life, were planned. This would have included the costs arising as a consequence of both true-positives and false-negatives and the costs of investigating incidental findings. Estimates of cost-effectiveness would have been taken as they were defined in the study and incremental cost per life-year or quality-adjusted life-year (QALY) were calculated if they could be estimated from the data reported.

In addition to our study eligibility criteria, economic evaluations had to meet the following inclusion criteria:

- compare a surveillance mammography regimen with an alternative follow-up regimen
- relate information on costs to effectiveness or have reported both cost and effectiveness data (in the same or separate study reports) for the reviewer to relate data on costs to effectiveness
- include detailed methods for estimating costs and effects data in the methods section of the study report and report the results in a results section.

Search methods for identification of studies

We conducted an extensive electronic search to identify reports of relevant published and ongoing studies, as well as any grey literature. The search strategies were designed to be highly sensitive, including both appropriate subject heading and text word terms to capture the concepts of surveillance mammography or other follow-up strategies and the study designs meeting the inclusion criteria for this review. The searches were restricted to full text papers published from 1990 onwards without language restriction. We searched the following databases for primary studies: MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, Science Citation Index (SCI), CANCERLIT and Cochrane Central Register of Controlled Trials (CENTRAL). We also searched the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the HTA Database for reports of evidence syntheses. Reports of ongoing and recently completed trials were sought from the Current Controlled Trials (CCT), Clinical Trials, WHO International Clinical Trials Registry Platform (ICTRP), NCI Clinical Trials Database, National Research Register (NRR) Archive, and NIHR Portfolio Database. *Appendix 10* gives full details of the search strategies used.

In addition, we searched relevant websites, namely those of the National Cancer Institute, National Comprehensive Cancer Network, CancerWEB, Breast Cancer Surveillance Consortium, and the National Library for Health, as well as relevant professional organisations including the American Society of Clinical Oncology, the American Society of Breast Disease, the American College of Radiology, and the European Society for Medical Oncology. We scanned reference lists of all included studies for additional reports.

Data extraction strategy

One reviewer (from GM, CR, RT and SZ) screened the titles and available abstracts of all reports identified by the search strategy for relevance to the inclusion criteria. One reviewer independently assessed full text copies of all potentially relevant studies to assess them for inclusion (from CB, CR and SZ). An economist reviewer examined reports relating to an economic evaluation or cost analysis.

We conducted a 10% check of inclusion assessment for all potentially relevant studies (RT). We resolved any disagreements by consensus or arbitration by a third party. A list of the included and excluded studies is given in *Appendices 11* and *12*, respectively.

One reviewer (from CR and SZ) independently extracted details of study design, participant characteristics, description of the intervention and outcome data (see *Appendix 13* for data extraction form). A second reviewer independently validated the data extraction (from CR and SZ). In the event of any uncertainty, a third reviewer advised on and validated the data extraction (CB).

Quality assessment strategy

We assessed the methodological quality of non-randomised studies using a quality assessment tool (*Appendix 14*) adapted from the Review Body for Interventional Procedures (ReBIP) checklist for quality assessment of non-randomised studies (comparative studies and case series). We included additional items (questions 18 and 19) to assess whether study authors attempt to correct for lead and length time bias in their analyses. Each of the items was checked as 'yes', 'no' or 'unclear'. Each item was worded so that a rating of 'yes' was the optimal rating of methodological quality, except item 14 regarding differential dropout rate/participants lost

to follow-up. We planned to use an adapted version of the Cochrane Collaboration's tool for assessing risk of bias[51] for assessing the methodological quality of individual RCTs. For the quality assessment of any economic evaluations, we planned to use the *NHS Economic Evaluation Database Handbook.*[52]

Data analysis

We planned statistical synthesis of results (using meta-analysis) of included studies directly comparing different surveillance mammography regimens or comparing surveillance mammography with an alternative follow-up regimen, for RCTs and non-randomised comparative studies, favouring intention to treat over per-protocol results for our analysis. We planned to derive a pooled HR for time-to-event outcomes (e.g. recurrence and survival). For data on harms of mammography, adverse events and quality of life we planned to use standardised mean difference to combine quality-of-life scores depending on the suitability of study data. We did not plan quantitative synthesis of economic outcomes data.

Results

Number and type of studies included and excluded

Figure 6 shows the number of potentially relevant studies identified by the search strategy with details of the number meeting the inclusion criteria and the number that were ineligible by exclusion criteria.

From the literature searches 2849 titles and abstracts were identified, 422 of which were selected for full text assessment. We excluded 414 reports, which did not meet the inclusion criteria for this review, of which we retained 114 reports to assess eligibility for inclusion in the systematic review of test performance (see *Chapter 5* of this report). Seven reports were unavailable. We list the bibliographic details of the eight studies that met the inclusion criteria in *Appendix 11*. We list the bibliographic details of the excluded studies, plus the reasons for exclusion in *Appendix 12*.

Characteristics of the included studies

Eight studies met our inclusion criteria.[53–60] *Appendix 15* provides full details of the characteristics of the included studies. Six studies[53–58] were retrospective cohort studies. Two studies[59,60] were prospective cohort studies. We did not identify any RCTs or economic evaluation studies meeting our inclusion criteria. Three studies[53–55] were conducted in the UK, whereas three[58–60] were conducted in the USA. The study by Paszat and colleagues[56] was conducted in Canada, and the study by Yau and colleagues[57] was conducted in China (Hong Kong). *Table 10* provides a summary of overall characteristics for the included studies. *Table 11* provides further details of the characteristics of individual studies.

As we lacked RCT studies directly comparing different surveillance mammography regimens we could not conduct a formal meta-analysis of these studies. In addition, none of the included studies compared surveillance regimens; therefore, it was not possible to undertake meta-analysis assessing surveillance regimens, including investigation of subgroup factors. Consequently, we decided to present a narrative synthesis of results for this review.

Four studies reported data for surveillance mammography only[56,58–60] and did not report details of any additional follow-up given to participants. Three studies considered surveillance mammography combined with clinical examination.[53–55] The study conducted by Yau and colleagues[57] considered surveillance mammography, combined with clinical and ultrasound examination of the breasts, conducted at the clinician's discretion. Six studies did not include
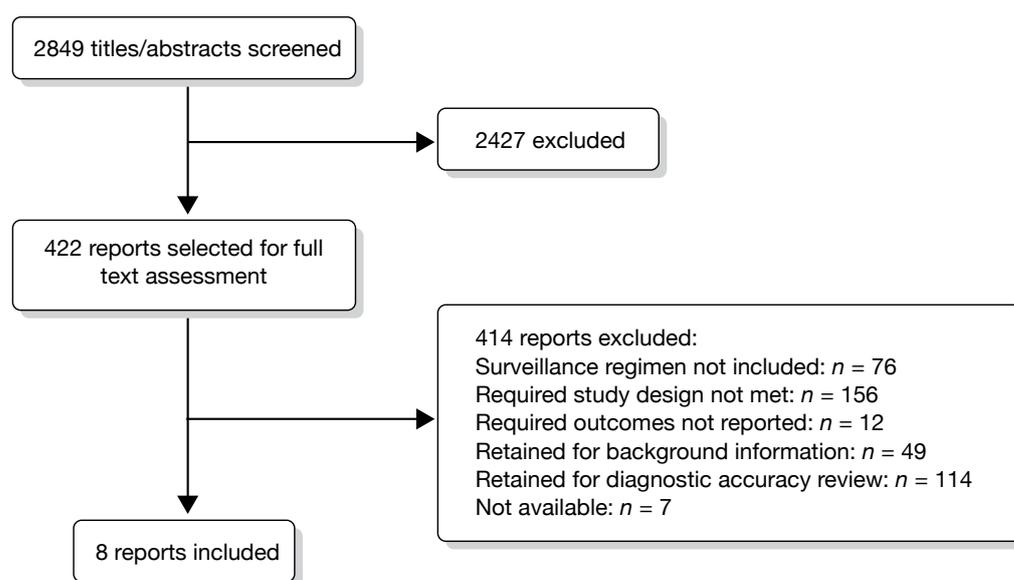
FIGURE 6 Flow chart of the number of potentially relevant reports of identified studies and the number subsequently included and excluded from the effectiveness review.

TABLE 10 Summary of the total number of patients and number of studies by study type, primary surgical treatment and type of surveillance test for the included effectiveness studies

Characteristic	No. of patients	No. of studies
Patients		
Enrolled	7337	8
Analysed	3775	
Type of study		
Prospective cohort	637	2
Retrospective cohort	3138	6
Type of primary surgical treatment		
Mastectomy	1190	5
Breast conserving	2571	8
No surgery	3	1
Information missing	9	2
Reported as 'other'	2	1
Type of surveillance test		
XRM	2350	4
Combined XRM, CE	918	3
Combined XRM, CE, US	507	1

CE, clinical examination; US, ultrasound; XRM, X-ray mammography.

a comparator regimen[53–55,57,58,60] Lash and colleagues[59] comparatively analysed the number of consecutive years of guideline surveillance (defined as annual history, annual clinical examination and annual surveillance mammography) received by women in their cohort with women who had not received consecutive years of guideline surveillance (i.e. women who

TABLE 11 Summary of characteristics for individuals effectiveness studies

Study ID	Study design	Type of primary surgical treatment	Type of surveillance test(s)	Description of surveillance regimen	Study comparator
Churn 2001[53]	Retrospective cohort	Mastectomy and breast conserving	CE, XRM	CE 3- to 4-monthly for first 2–3 years, 6-monthly for up to 5 years, annually thereafter. Alternate appointments with surgical and oncological teams for 3–5 years, followed by discharge to continue follow-up in one or other clinics. XRM according to individual clinician preference (usually less frequently than annually)	None
Lash 2005[59]	Multicentre prospective cohort			Guideline surveillance – defined as annual CE and XRM for patients with asymptomatic history	No. of consecutive years of receipt of guideline surveillance compared with not receiving guideline surveillance
Lash 2006[60]			XRM	Presumed guideline surveillance – defined as annual examination for patients with asymptomatic history, physical examination and XRM	No. of XRMs received by women who died (all-cause mortality) compared with the number of XRMs received by women who did not die
Lash 2007[58]	Retrospective cohort			Presumed guideline surveillance – defined as annual CE and XRM for patients with asymptomatic history	No. of XRMs received by women who died (all-cause mortality) compared with the number of XRMs received by women who did not die
Montgomery 2007[54]		Breast conserving	CE, XRM	Outpatient CE performed 3- to 4-monthly for first 2 years, 6-monthly for 3 years, then annually until 10 years post primary treatment from 1991 to 1998. From 2000, all patients received annual CE. Annual bilateral XRM performed. All patients instructed in breast self-examination. Additional interval visits as required	None
Montgomery 2009[55]				Outpatient CE performed 3- to 4-monthly for first 2 years, 6-monthly for 3 years, annual visits until 10th anniversary thereafter. From 2000 all patients received annual CE. Additional interval visits. Annual bilateral XRM. Patients usually discharged to the national breast-screening unit at 10 years	Survival for CE-detected tumour compared with survival for XRM-detected tumour
Paszat 2008[56]		Mastectomy and breast conserving	XRM	Presumed guideline surveillance – defined as annual CE and XRM for patients with asymptomatic history	No. of XRMs received compared with no receipt of XRM
Yau 2008[57]		Breast conserving	CE, XRM	CE every 2–3 months in the first 2 years, every 4–6 months in the third to fifth years, annually thereafter. Annual bilateral XRM for first 5 years, once every 1–2 years for next 5 years. Supplementary ultrasound at clinician's discretion	None

CE, clinical examination; NR, not reported; XRM, X-ray mammography.

had missed one or more annual surveillance appointment for unspecified reasons). Paszat and colleagues[56] compared women in receipt of more than one episode of surveillance mammography within their cohort with women who did not receive surveillance mammography.

Overall, the eight studies enrolled 7337 patients. After exclusions, due to eligibility or participant dropout, the studies included 3775 patients in their analyses. The studies included 1626 mastectomy patients and 4864 breast conservation surgery patients all treated for primary breast cancer and without detectable metastatic disease. Five studies[53,56,58–60] reported participant age details, with 444 participants aged < 50 years and 4168 participants aged 50 years or older. Two studies[54,55] reported mean ages, 56 and 58 years, and age ranges, 24–91 and 28–91 years, respectively. Yau and colleagues[57] reported a median age of 46 years and range 25–90 years. The earliest report was published in 2001[53] and the latest in 2009.[55] The earliest date of primary treatment reported was 1990[58] and the latest was 2003.[57] Follow-up ranged from 2.4 months to 15 years.

Quality of the included studies

The results of the quality assessment for the individual studies are shown in *Appendix 16*. *Figure 7* summarises the quality assessment of the included studies.

Four studies[56,58–60] were considered to include samples that were unrepresentative of those women who we considered eligible for surveillance mammography (i.e. all women treated for primary breast cancer). Three of these studies, conducted by the same lead author,[58–60] included only women aged over 65 years. It is unclear whether the cohorts of women included in the studies conducted in 2005[59] and by Lash and colleagues[58] included the same women and hence whether or not the studies had an overlap of patients. This older age group represents only a proportion of what we consider the eligible population. A pragmatic surveillance mammography regimen could include women of all ages, with those over the age of 50 years possibly benefiting from eligibility for inclusion in the national NHSBSP. In addition, we also considered that the sample included in the study conducted by Paszat and colleagues[56] was unrepresentative. In this study, the authors randomly selected two samples from their previously identified population of women treated for
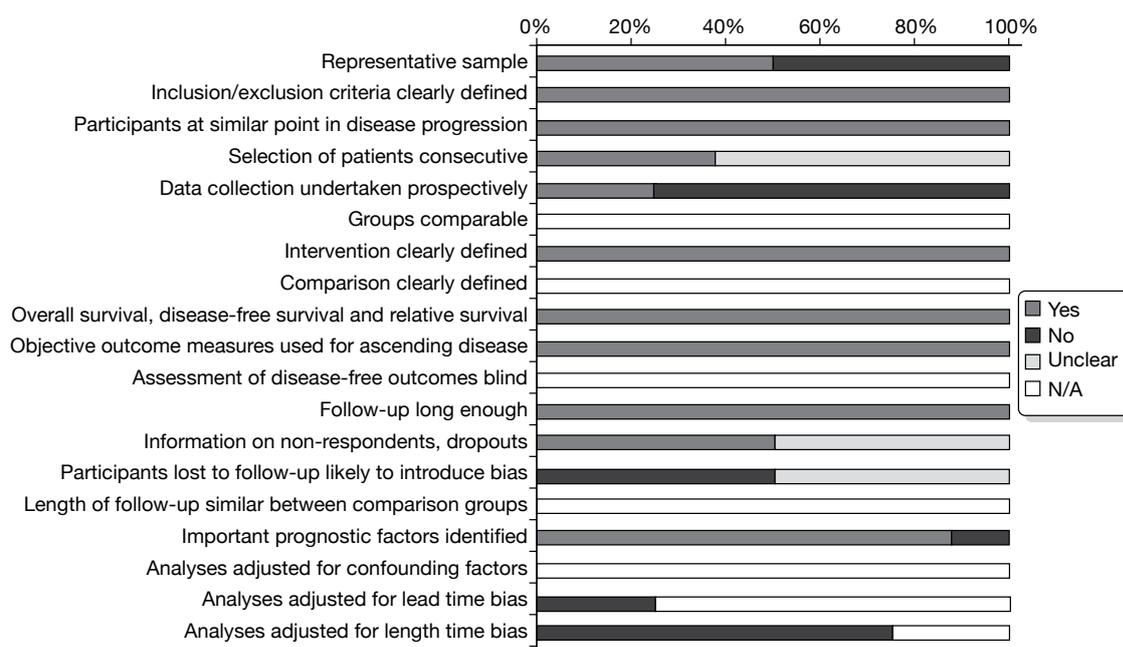
FIGURE 7 Summary of quality assessment of the included effectiveness studies.

primary breast cancer. The authors drew one random sample from women without any further breast surgery after their initial primary treatment. A larger second sample was drawn from the same group who had undergone further breast surgery 6 or more months after their initial treatment. The second sampling fraction was larger (0.237 compared with 0.055) to increase the probability of including women with an episode of IBTR and/or MCBC. We therefore considered that this second group of women with subsequent breast surgery were over-represented in comparison to our study population.

It was unclear for five reports[53,55–58] whether participants were a consecutively treated series of patients, whereas in three studies[54,59,60] patient selection was consecutive. All studies clearly described their inclusion/exclusion criteria and the intervention, and avoided disease progression bias by enrolling participants who were all at a similar point in their condition, as opposed to including patients at mixed levels of advancement in their cancer. All studies used objective outcome measures for ascertaining overall and disease-free survival, and mortality and IBTR/MCBC event rates. All studies included a median follow-up time of at least 5 years, which we considered adequate for detecting important outcome effects. We did not consider lead and length time bias to be applicable to the studies by Montgomery and colleagues[55] and Yau and colleagues[57] as neither study reported mortality data. The remaining studies did not adjust for lead or length time bias in their analyses.

Four studies[54,55,59,60] provided information on non-respondents and dropouts (e.g. incomplete case note data, losses to follow-up, etc.) and all were judged to have avoided attrition bias, defined as bias introduced by high or differential dropout of patients. This information was judged as being unclear in the remaining studies.[53,56–58] All but one study[54] identified important prognostic factors for patients' overall survival or mortality.

Two studies[59,60] undertook prospective data collection, whereas the remainder undertook retrospective data review.[53–58]

Assessment of effectiveness

Two studies provided data on overall survival, cause-specific survival and the annual hazard rate of ipsilateral locoregional and new contralateral relapse in graph form.[54,55] Those remaining reports eligible for inclusion in this review reported numbers of overall deaths,[53,56,58–60] deaths due to breast cancer[53,56,58–60] and IBTR and/or MCBC events only.[53,56–58]

Overall survival and mortality

Table 12 summarises the data for mortality as reported by the individual studies. For breast cancer-specific mortality, four studies[53,56,59,60] did not report whether deaths were due to primary breast cancer, breast cancer recurrence or a second primary cancer. Two studies[54,58] reported deaths due to recurrent cancer or a second primary cancer.

Churn and colleagues[53] reported 112 deaths from all causes from an analysis of 612 women.

Lash and colleagues[59] reported 63 deaths from all causes from an analysis of 303 women. Of these deaths, 27 were due to breast cancer. For all-cause mortality the authors reported a crude conditional odds ratio (OR) of 0.62 [95% confidence interval (CI) 0.48 to 0.80] for the effect of a consecutive year of mammographic surveillance with clinical examination compared with lack of consecutive years of surveillance (i.e. women did not receive surveillance at each consecutive year). The age-adjusted OR was reported as 0.66 (95% CI 0.51 to 0.86). For breast cancer-specific mortality an OR of 0.7 (95% CI 0.52 to 1.1) was reported. For all but breast cancer mortality, the OR was 0.69 (95% CI 0.48 to 0.99).

TABLE 12 Numbers of deaths due to all causes, breast cancer and IBTR/MCBC, as reported by the included effectiveness studies

Study ID	No. of patients studied	All-cause mortality		Breast cancer-specific mortality		IBTR/MCBC specific		Follow-up time for whole cohort
		n/N	%	n/N	%	n/N	%	
Churn 2001[53]	612	112/612	18		NR		NR	5 years
Lash 2005[59]	303	63/303	21	27/303	9		NR	Median 7.4 years (range 10 months to 9.5 years)
Lash 2006[60]	334	32/334	10	13/334	4		NR	5–8 years
Lash 2007[58]	812	391/812	48	178/812	22	130		5 years
Montgomery 2007[54]	110		NR		NR	24/110	22	Median 10 years (range 1.5–15 years)
Montgomery 2009[55]	196		NR		NR		NR	Median 5.9 years (range 4 months to 10.5 years)
Paszat 2008[56]	901	512/901	57	374/901	42		NR	15 years
Yau 2008[57]	507		NR		NR		NR	Median 5.9 years (range 0.2–13 years)

Lash and colleagues[60] reported 32 deaths from all causes from an analysis of 334 women. Of these deaths, 13 were due to breast cancer. The authors reported a decline in mortality rate with increasing number of surveillance mammograms received (p for trend = 0.007). The crude OR for an additional surveillance mammogram compared with no surveillance mammography was 0.79 (95% CI 0.56 to 1.1). After adjusting for age, primary tumour stage and receipt of adjuvant tamoxifen treatment, this figure was reported as 0.77 (95% CI 0.53 to 1.1). The authors stated that they had insufficient data to analyse the effect of surveillance mammography on breast cancer-specific mortality rates.

Lash and colleagues[58] reported 391 deaths from all causes and 178 deaths due to breast cancer within the first 5 years of follow-up. Of those women dying from breast cancer, 130 had experienced breast cancer recurrence. Thirteen of these recurrences were local and five of the women received a surveillance mammogram in the preceding year (38%). In addition, 101 women had a recurrence and did not die from breast cancer. Of these women 24 had a local recurrence, of whom 19 received a surveillance mammogram in the preceding year (79%).

Montgomery and colleagues[54] reported a series of 1312 patients who were treated by breast conservation surgery. There were 116 patients with an isolated local recurrence and from this group 110 were available for analysis (attrition due to either incomplete case notes or patients lost to follow-up). In this group of 110 patients, two patients had ipsilateral breast relapse diagnosed incidentally during breast reshaping procedures, both of whom subsequently died. Thirty-five of the remaining 108 women died. Of these 35 deaths, 12 had IBTR recurrence, 11 had ipsilateral axillary recurrence, three had recurrence in both the breast and axilla, eight had MCBC and one patient had bilateral breast (IBTR and MCBC) recurrence.

Paszat and colleagues[56] reported 512 deaths, of which 374 were breast cancer specific, from an analysed study population of 901 patients. The authors analysed the association between exposure to one or more episodes of surveillance mammography and the risk of death. Adjusting for age, tumour stage, surgery, and adjuvant chemotherapy and adjuvant tamoxifen treatment, the authors reported a HR of 0.28 (95% CI 0.22 to 0.37) for breast cancer-specific death. Of those

women with IBTR the authors reported an unadjusted HR of 0.36 (95% CI 0.13 to 1.00). The authors reported an unadjusted figure of 0.86 (95% CI 0.20 to 3.77) for women with MCBC.

The remaining studies[55,57] did not report survival data.

IBTR and/or MCBC event rate

Table 13 summarises the data for IBTR and/or MCBC event rates as reported by the individual studies. Two studies did not report details of IBTR and/or MCBC recurrence and are therefore excluded from this table.[59,60] The remaining six studies[53–58] did not report raw data time points for when IBTR and/or MCBC events occurred but reported numbers of individual IBTR and/or MCBC events experienced within the individual cohort. We have not included any recurrences occurring outside the breast in *Table 13*, for example regional (axillary) recurrences or distant metastatic recurrences. Details of these recurrence events are available in *Appendix 15* if reported by individual study authors.

Lash and colleagues[58] reported details for locoregional recurrence. We were able to identify 37 cases of IBTR recurrence in this study but were unable to identify numbers with MCBC only. Montgomery and colleagues[55] reported one case of MCBC in the first year following treatment of the primary breast cancer, with a case of IBTR and one case of MCBC within the first 3 years; with a further three IBTR and four MCBC cases occuring 3 years after treatment.

Method of detection

Five studies[53–57] reported details of the mode of IBTR/MCBC detection where this was known. The study conducted by Montgomery and colleagues[55] reports subsequent deaths where known. *Table 14* summarises this data. The remaining studies[58–60] did not report data regarding the method of detection.

We did not find any studies meeting our inclusion criteria that reported data on quality of life, harms of mammography, uptake of mammography or economic data.

TABLE 13 Number of patients diagnosed with IBTR/MCBC as reported by the included effectiveness studies

| Study ID | No. of patients studied | Nos. of patients diagnosed with: | | | | | | Follow-up time for whole cohort |
| | | IBTR | | MCBC | | Bilateral IBTR and MCBC | | |
		n/N	%	*n/N*	%	*n/N*	%	
Churn 2001[53]	612	25/505	5	9/104	9	0	0	5 years
Lash 2007[58]	812	37/851	4[a]		NR		NR	5 years
Montgomery 2007[54]	110	48/110	44	35/110	32	2/110	2	Median 10 years (range 1.5–15 years)
Montgomery 2009[55]	196	4/196	2	6/196	3	0	0	Median 5.9 years (range 4 months to 10.5 years)
Paszat 2008[56]	901	84/584	14	49/317	16	0	0	15 years
Yau 2008[57]	507	23/507	5	13/507	3	0	0	Median 5.9 years (range 0.2–13 years)

a   Overall, 851 BCS patients and 973 mastectomy patients were enrolled in this cohort and 812 patients were analysed. Breakdown of surgery type included in the analysis is not given.

TABLE 14 Method of IBTR/MCBC detection as reported by the included effectiveness studies

Study ID	Method of first detection	No. of IBTRs detected		No. who died		No. of MCBCs detected		No. who died		No. of bilateral IBTRs/ MCBCs detected		No. who died	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Churn 2001[53]	Surveillance mammography	7/25	28			0/9	0						
	Clinical examination	8/25	32			4/9	44						
	Other	10/25	40			5/9	56						
Montgomery 2007[54]	Surveillance mammography	25/46	54	6/25	24	25/35	71	5/25	20	2/2	100	1/2	50
	Clinical examination	4/46	9	4/4	100	2/35	6	0		0		0	
	Symptomatic interim referral	12/46	26	4/12	42	5/35	14	1/5	20	0		0	
	Symptoms	5/46	11	1/5	20	3/35	9	2/3	67	0		0	
Montgomery 2009[55]	Surveillance mammography	0/4	0			3/6	50						
	Clinical examination	1/4	25			2/6	33						
	Other	3/4	75			1/6	17						
Paszat 2008[56]	Surveillance mammography	33/84	39			24/49	49						
	Other	51/84	61			25/49	51						
Yau 2008[57]	Surveillance mammography	10/23	44			8/13	62						
	Clinical examination	8/23	35			3/13	23						
	Symptomatic interim referral	2/23	9			1/13	8						
	Supplementary ultrasound	2/23	9			1/13	8						
	Other	1/23	4			0/13	0						

Summary

We conducted a systematic review to determine the clinical effectiveness of differing surveillance mammography regimens in detecting IBTR and MCBC in women who were previously diagnosed and treated for primary breast cancer without metastatic disease from 1990 onwards. We aimed to include RCT and non-randomised comparative studies of differing surveillance mammography and alternative breast cancer follow-up regimens. We also included prospective and retrospective cohort studies of differing surveillance mammography regimens or alternative breast cancer follow-up regimens containing 100 or more participants, where participants were followed up for at least a median time of 5 years. The methods used for conducting this review are systematic, explicit and comprehensive, and our inclusion criteria are both clinically relevant and scientifically rigorous.

Despite extensive searching, we identified only eight studies that met our inclusion criteria, all of which were cohort studies. Furthermore, none of the regimens described in these studies was identical. For this review, we sought data from the included studies on eight outcomes but for six of these outcomes no data were available. Only two studies[54,55] provided time-to-event data for overall and disease-free survival in graph form. In terms of numbers of patients alive and dead, only five studies contributed data towards this outcome.[53,54,56,59,60] Only six studies reported data on numbers of patients experiencing IBTR and/or MCBC events.[53–58] The paucity of the underlying evidence base mirrors the findings of previous reviews[4,29,43–47] described earlier. Nevertheless, a number of conclusions may be drawn.

Firstly, there is a suggestion from two studies that surveillance mammography offers a protective effect against death from all causes.[59,60] The data reported by Paszat and colleagues[56] also suggest a protective effect of surveillance mammography for breast cancer-specific death. Furthermore, the data reported by Montgomery and colleagues[54] suggest a protective effect against death for surveillance mammography-detected IBTR when compared with clinical examination, although numbers of patients and events are small. In addition, the Montgomery data suggest that a high proportion of patients (20%) were recalled in between routine appointments, in most cases to report a recurrence detected by the patients themselves. As the remaining studies did not include a comparator for surveillance mammography, neither in frequency, nor with an alternative regimen, it is not possible to make recommendations for the effectiveness of any surveillance regimen beyond these three studies.

Few studies met our eligibility criteria and those included in this review are prone to lead and length time bias. The limited and variable nature of the data provided by the included studies precluded formal quantitative synthesis, thus only a narrative synthesis of evidence was possible. The predefined inclusion criteria for this review did not include measures of psychological effects, which are known to be important to the patient experience of surveillance. We further discuss key findings and limitations of this review in *Chapter 8*.

Chapter 5

Systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

Overview

Introduction

The aim of this review was to determine the diagnostic accuracy of surveillance mammography for detecting IBTR and MCBC in women who were previously treated for primary breast cancer.

- *Primary objective* To determine the performance of surveillance mammography, alone or in combination with other tests, in detecting IBTR and/or MCBC in women undergoing routine surveillance.
- *Secondary objective* To determine the performance of surveillance mammography, alone or in combination with other tests, compared with alternative tests, alone or in combination, in detecting IBTR and/or MCBC in women with a prior diagnostic test result indicating suspicion of IBTR and/or MCBC (referred to subsequently as non-routine surveillance).

Methods

Inclusion and exclusion criteria

Types of study

The following types of study were considered for inclusion:

- RCTs in which women are randomised to receive either the index or comparator test(s) and all receive the reference standard test.
- Diagnostic consecutive cohort studies in which both index and comparator tests are evaluated against the reference standard test in the same women within the study (head-to-head design).
- Indirect (between-study) comparisons by comparing cohort studies where women received either the index test, or the comparator test, or a combination of tests with the reference standard test, and where at least 100 participants were included in the analysis of test performance. This type of study design is less reliable than direct studies, as differences in diagnostic accuracy are susceptible to confounding factors between studies.[61]

We did not consider case reports and studies investigating technical aspects of a test.

Types of participants

The types of participants considered were women previously treated for primary breast cancer without detectable metastatic disease at initial presentation.

Index test
The index test was surveillance mammography.

Comparator test(s)
The following comparator tests were considered:

- ultrasound
- magnetic resonance imaging
- specialist-led clinical examination:
  - hospital clinician led
  - hospital nurse led
- unstructured primary care follow-up (here defined as absence of formal routine secondary care follow-up, which may, or may not, involve mammography)
- GP-led follow-up:
  - self-presentation
  - self-examination.

We planned to consider comparisons of both individual and combinations of tests. We considered test performance in all settings.

Target condition
The target condition was IBTR and MCBC following treatment for primary breast cancer. For the purposes of diagnostic test accuracy, we made no distinction between detection of ipsilateral recurrent breast tumours and ipsilateral second primary tumours.

Reference standard
Histopathological examination is the commonly agreed reference standard for diagnosing recurrent breast cancer based on tissue obtained by biopsy, usually as a needle biopsy under local anaesthesia or in some patients following a surgical biopsy. In addition, in some breast clinics, fine-needle aspiration cytology (with or without immediate reporting) is available to allow a diagnosis of recurrence. This is usually confirmed by biopsy. Cytological and/or histopathological examination is undertaken if suspicion of malignancy is raised on a surveillance test. In contrast, there is no reference standard for ascertaining the true-negative and false-negative measures of a surveillance test for recurrent breast cancer, although this is usually ascertained by a negative result or a positive test result at subsequent testing after a period of follow-up has elapsed (e.g. 1-year mammography interval, 2- to 3-year MRI interval, etc.). A pragmatic reference standard is therefore diagnosis of IBTR or MCBC that occurs within a 3-year period of conducting a surveillance test.

The reference standard for this review was histopathological assessment for test positives, along with a follow-up period of up to 3 years for test negatives (in order to differentiate between true-negatives and false-negatives).

Outcomes
The following types of outcome were considered.

Test performance in diagnosing:

- IBTR in women undergoing routine surveillance
- IBTR in women undergoing non-routine surveillance
- MCBC in women undergoing routine surveillance
- MCBC in women undergoing non-routine surveillance.

To be considered for inclusion, the studies had to report the absolute numbers of true-positives, false-positives, false-negatives and true-negatives, or provide information allowing their calculation, and report a per-patient analysis.

In studies reporting the above outcomes, we planned to record the following additional outcomes, if reported:

■   adverse effects (defined as physical harms) of mammography and other tests
■   acceptability of the tests
■   reliability of the tests
■   radiological/operator expertise (who conducts the test and previous experience)
■   interpretability/readability of the tests.

Search strategy

Electronic searches were conducted to identify reports of published, unpublished and ongoing studies. The search strategies were designed to be highly sensitive, including both appropriate subject heading and text word terms to identify diagnostic accuracy studies of mammography and comparative tests when used in surveillance. To ensure data consistency with other areas of this project, searches were restricted to English-language reports published from 1990 onwards. Conference abstracts were not included. The following databases were searched for primary studies: MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, SCI and CANCERLIT, whereas Medion, the CDSR, DARE and the HTA database were searched for reports of evidence syntheses. Reports of ongoing and recently completed trials were sought from the CCT, Clinical Trials, WHO ICTRP, NCI Clinical Trials Database, NRR Archive and NIHR Portfolio Database. *Appendix 17* gives full details of the search strategies used.

In addition, relevant websites were searched and included the National Cancer Institute, National Comprehensive Cancer Network, CancerWEB, Breast Cancer Surveillance Consortium, and National Library for Health, as well as relevant professional organisations including the RCR, ABS at the BASO, American Society of Clinical Oncology, American Society of Breast Disease, American College of Radiology, and European Society for Clinical Oncology. The reference lists of all included studies were also scanned for additional reports.

Data extraction strategy

One reviewer (from FG, GM, CR, SKA, RT or SZ) screened the titles and abstracts (if available) of all reports identified by the search strategy. One reviewer (from FG, JH, GM, CR, SKA, RT or SZ) assessed potentially relevant full text studies for inclusion. One reviewer (RT) conducted a 10% check of the inclusion assessment for all potentially relevant studies. Any disagreements were resolved by consensus or arbitration by a third party.

One reviewer (from JH, CR, SKA or SZ) independently extracted details of study design, participants, index, comparator and reference standard tests, and participant flow and outcome data (see *Appendix 18* for details of the data extraction form). A second reviewer independently validated the data extraction. In the event of any uncertainty regarding the data extraction, a third reviewer gave advice and validated the data extraction (CB).

Quality assessment strategy

Two reviewers (from JH, CR, SKA or SZ) independently assessed the methodological quality of all included studies, using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (*Appendix 19*).[62] QUADAS is a quality assessment tool for assessing the methodological quality of individual studies in systematic reviews of diagnostic accuracy. It is designed to be adapted to make it applicable to a specific review topic. QUADAS was developed

through a formal consensus method and was based on empirical evidence. The original QUADAS checklist contained 14 questions. We adapted the QUADAS tool to make it more applicable for assessing reports of tests for IBTR/MCBC. We omitted three questions in the original QUADAS tool that related to the quality of reporting rather than methodological quality (questions 2, 8 and 9). These questions related to the description of (1) the selection criteria; (2) the execution of the index test; and (3) the execution of the reference standard test.

In question 1 we defined the spectrum of patients representative of those receiving the test in practice as women of all ages previously treated for primary breast cancer, without detectable metastatic disease. We defined the reference standard (question 2) of the modified tool as histopathological assessment for correctly identifying the target condition. We did not include follow-up time in this question, as follow-up alone will only identify a possible false-negative result but will not identify the target condition as a stand-alone test. We split question 3 (disease progression bias) into two parts for (1) test positives and (2) test negatives to assess whether the target condition was likely to have changed between the test and the two types of reference standard test. We split question 5 (differential verification bias) to assess whether (1) all test positives were verified by histopathological assessment and (2) whether all test negatives received appropriate follow-up. We added an additional item (question 9) to assess whether the index and comparator tests were independently interpreted.

We did not change the remaining questions. These concerned partial verification bias (question 4), incorporation bias (question 6), test review bias and diagnostic review bias (questions 7 and 8), clinical review bias (question 10), reporting of uninterpretable/intermediate results (question 11) and attrition bias (question 12).

Any disagreements were resolved by consensus or arbitration by a third party. Each of the items was checked as 'yes', 'no' or 'unclear'. Each item was worded so that a rating of 'yes' was the optimal rating of methodological quality. A study was considered to be of higher quality if it was checked as 'yes' to items assessing patient spectrum, partial verification and differential verification bias and test review bias. We planned to use a separate quality assessment tool using a checklist adapted from Verhagen and colleagues[63] for any RCTs.

Data analysis

The results of the individual studies were tabulated into a 2×2 table, and sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio (DOR) were calculated along with 95% CIs. The intention was to combine the results of the included studies in a meta-analysis using the hierarchical summary receiver operating characteristic (HSROC) framework, where three or more studies reported sufficient data. However, due to limited data and variability across studies, we felt it unwise to perform a meta-analysis and therefore a narrative synthesis of the results is presented (see *Table 16* and *Appendix 22* for summary characteristics of the included studies).

Results

Number and type of studies included and excluded

Nine studies met our inclusion criteria. *Figure 8* shows the number of potentially relevant reports of the studies identified, the number included and excluded and a summary of the exclusion criteria. *Appendix 20* lists the bibliographic details of the nine studies that were included in the review.

The bibliographic details of the potentially relevant studies identified by the search strategy, for which full text papers were obtained, but which subsequently failed to meet the inclusion criteria, are given in *Appendix 21*. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of types of studies, participants, test, reference standard or outcomes (see also *Figure 8*).

Characteristics of the included studies

Appendix 22 provides details of the characteristics of the included studies. *Table 15* provides a summary of the overall characteristics of the included studies. *Table 16* provides further details of the characteristics of study design, patient type, considered index/comparator test and follow-up periods for verifying test-negative results for the individual studies arranged alphabetically by author.

Overall, the nine studies enrolled 4002 participants. After exclusions, due to eligibility or participant dropout, the studies included 3724 participants in their analyses. The earliest study took place in 1995[64] and the latest in 2009.[65] The earliest participant enrolment date given was 1992[64] and the latest was 2003.[65] Four studies did not give any indication of the enrolment time period.[66–69] One study took place in Sweden,[64] two in the UK,[67,68] two in Germany,[69,70] two in South Korea,[65,71] one in Italy[66] and one in France.[72] The ages of the participants ranged from 22 to 82 years.[65] Most participants were aged in their fifties. Details of mean, with standard deviations (SDs), and median ages for individual studies are shown, where these were reported, in *Appendix 22*. Reported follow-up of test negatives ranged from 5 to 32 months.

The studies by Rieber and colleagues[69] and Shin and colleagues[71] were cohort studies, in which participants received a comparator test (MRI in the study by Rieber and colleagues[69] and ultrasound in the study by Shin and colleagues[71]) and the reference standard. The seven remaining studies[64–68,70,72] were direct head-to-head studies, in which participants all received the index test, comparator test and reference standard.
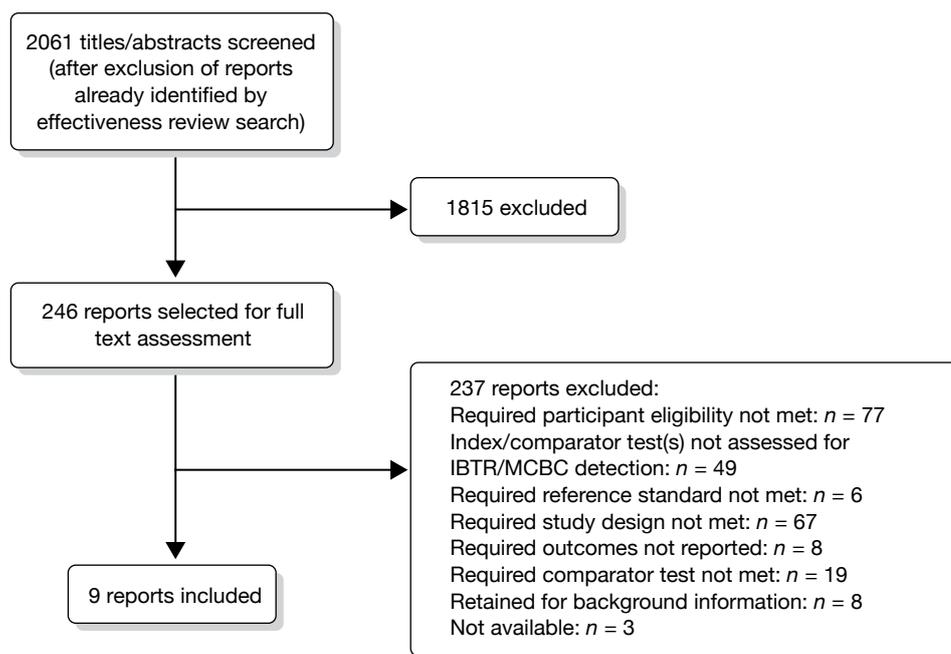
FIGURE 8 Flow chart of the number of potentially relevant reports of identified studies and the number subsequently included and excluded from the diagnostic accuracy review.

TABLE 15 Summary of the total number of patients and number of studies by type of study, numbers analysed, type of surveillance and focus of surveillance for the included diagnostic accuracy studies

Characteristic	No. of patients (%)	No. of studies (%)
Type of study		
Cohort	2108	2 (22)
Head to head	1616	7 (78)
Patients		
Enrolled	4002	9
Analysed	3724	
Type of surveillance		
Routine surveillance	3451 (93)	6 (77)
Non-routine surveillance	273 (7)	3 (33)
Focus of surveillance		
Local recurrence (IBTR)	298 (8)	5 (56)
Contralateral recurrence (MCBC)	1375 (37)	2 (22)
Both	2051 (55)	2 (22)
Type of test[a]		
XRM	344	5
US	2094	3
MRI	500	6
CE	314	4
Combined XRM, CE	105	1
Combined XRM, US	1256	1
Combined XRM, CE, US	119	1
Combined XRM, CE, US, MRI	119	1

CE, clinical examination; US, ultrasound; XRM, X-ray mammography.
a   Multiple tests used within studies.

In breast cancer surveillance, the considered diagnostic tests can be used at different stages in the assessment pathway prior to a positive test result receiving verification via the reference standard test. As described earlier, test administration may be as a first routine surveillance test in a patient with no prior suspicion of IBTR/MCBC, or it may be used to evaluate a suspicious test finding on a prior diagnostic test (non-routine surveillance patients). Six studies assessed performance of the diagnostic test used as a routine first surveillance test.[64–67,70,71] The three remaining studies, by Mumtaz and colleagues,[68] Rieber and colleagues[69] and Ternier and colleagues,[72] assessed the performance of the diagnostic test as part of non-routine surveillance to evaluate a suspicious result from a prior diagnostic test.

Three studies reported data on ultrasound.[66,71,72] Six studies reported data on MRI.[64,66–70] Four reported data on specialist-led clinical examination.[64,66,67,72] The studies did not explicitly state whether a hospital-based consultant or an alternative health-care professional conducted the clinical examination. We assumed in all cases that the examination was conducted at a consultant-supervised clinic. Drew and colleagues[67] reported test performance for surveillance mammography, combined with clinical examination. Viehweg and colleagues[70] reported test performance for combined surveillance mammography, clinical examination and ultrasound (known as conventional methods). This study also reported performance for combined MRI and

TABLE 16 Summary of characteristics for individual diagnostic accuracy studies

Study ID	Study design	Type of primary surgery	Index tests	Comparator test	Follow-up time for verifying test-negative results
Belli 2002[66]	Direct head-to-head cohort	Non-routine surveillance BCS patients	MRI for local recurrence	XRM, CE, US for local recurrence	MRI and CE follow-up performed at 3 months All MRI test negatives underwent cytological examination
Boné 1995[64]		Routine surveillance mastectomy patients, all with breast reconstruction and implants	XRM for local and contralateral recurrence	MRI, CE for local and contralateral recurrence	Median 10 months (range 5–18 months)
Drew 1998[67]		Routine surveillance BCS patients	MRI for local recurrence	XRM, CE, XRM + CE for local recurrence	Median 341 days (range 168–451 days)
Kim 2009[65]		Routine surveillance breast-conserving and mastectomy patients	Adjunct US (XRM + US) for contralateral recurrence	None	1–2 years
Mumtaz 1997[68]		Non-routine surveillance BCS patients	XRM for local recurrence	MRI for local recurrence	Median 12 months (range 6–15 months)
Rieber 1997[69]	Cohort		MRI for local recurrence	None	CE, US performed at 6-month follow-up. XRM performed at 12-month follow-up. In 22 patients a control MRI was performed at intervals of 2–16 months (mean 7.2 months)
Shin 2005[71]		Routine surveillance patients (primary surgery type not reported)	US for local and contralateral recurrence	None	6 months
Ternier 2006[72]	Direct head-to-head cohort	Non-routine surveillance BCS patients	XRM for local recurrence[a]	CE, US for local recurrence	6 months
Viehweg 2004[70]		Routine surveillance BCS patients	MRI for contralateral recurrence	CM (XRM + CE + US); MRI + CM for contralateral recurrence	12 months

CE, clinical examination; CM, conventional methods; NS, not stated; US, ultrasound; XRM, X-ray mammography.
a   Study authors considered computerised tomography as the index test in this study, but this test was not considered as an included comparator in this review.

conventional methods. Kim and colleagues[65] reported performance for combined surveillance mammography and ultrasound. None of the studies meeting our inclusion criteria reported data on unstructured primary care follow-up.

The study by Boné and colleagues[64] involved mastectomy patients who had all received breast reconstruction with implants. Currently, these patients are offered clinical follow-up for the ipsilateral breast and surveillance mammography for the contralateral breast annually or once every 2 years. Surveillance mammography of the ipsilateral reconstructed breast is performed if there is a clinical concern. A previous systematic review of surveillance mammography following breast reconstruction was published in 2007 by Barnsley and colleagues.[43] This review considered case reports and case series literature published between January 1980 and August 2004. The included studies involved implants and immediate or delayed transverse rectus abdominis muscle (TRAM) flap reconstructions. The authors did not conduct a meta-analysis due to heterogeneity in study design, follow-up and surveillance mammography regimen. Review findings suggested

that surveillance mammography is able to detect certain local recurrences, although the authors concluded that, due to the paucity of evidence, further research in this area is required. We therefore believe that this study merits inclusion in our review, as, although these women represent a subset of our considered population, they are an increasingly relevant subgroup who might receive surveillance mammography in the future.

Quality of the included diagnostic accuracy studies

The results of the quality assessment for the individual studies are shown in *Appendix 23*. *Figures 9* and *10* summarise the quality assessment of the included studies.

None of the studies met all of our quality criteria specified for higher-quality studies, although in five studies[65,66,68,69,72] this was due to lack of clarity as to whether reference standard results were interpreted without knowledge of index test results only.

The study conducted by Boné and colleagues[64] was considered to be unrepresentative of our considered patient population as a whole; as previously discussed, the participants had all received mastectomy for primary breast cancer with breast reconstruction and implants. As discussed earlier, it is not standard practice to offer routine surveillance of the treated breast to patients receiving either mastectomy alone, or mastectomy with breast reconstruction and implants. We therefore felt that, although this patient group represents a subset of our considered population, they differ from the wider spectrum of women who would receive surveillance in practice.

Only the Shin and colleagues[71] study was judged as free of disease progression bias for positive index test results. Disease progression bias occurs when the time delay between the index and reference standard test is such that improvement or progression of the condition may occur in the intervening period. It was unclear whether the remaining eight (89%) studies[64–70,72] had
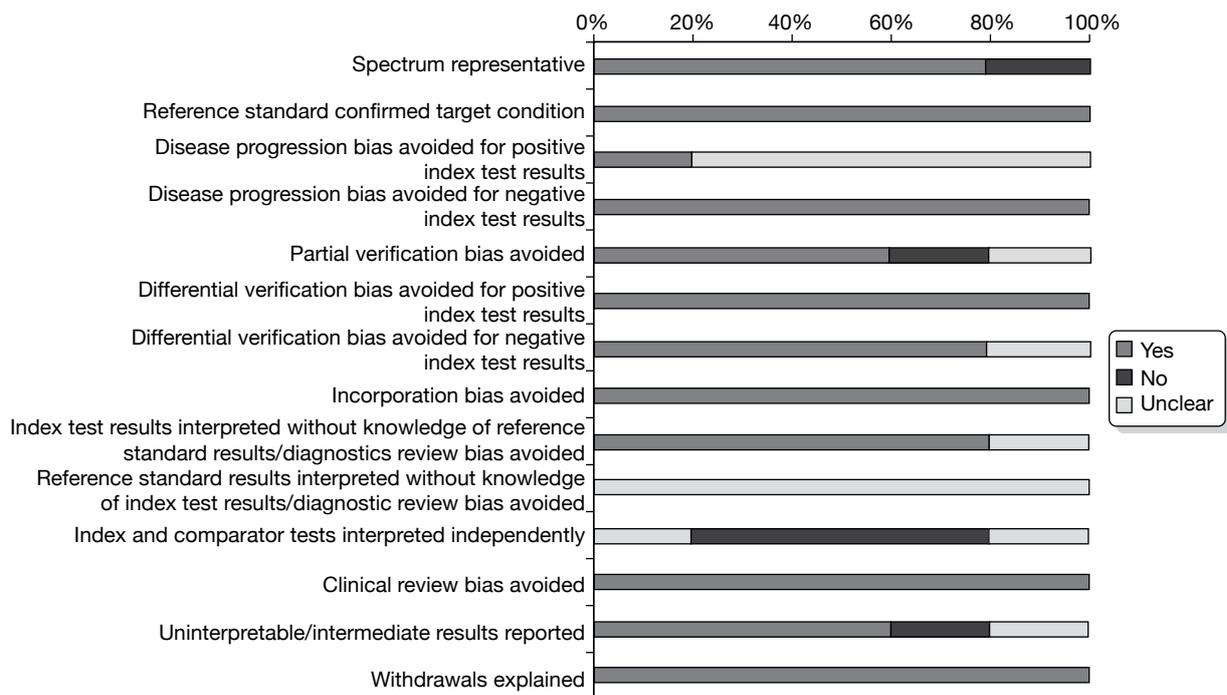
FIGURE 9 Summary of quality assessment of included diagnostic accuracy studies for routine surveillance.
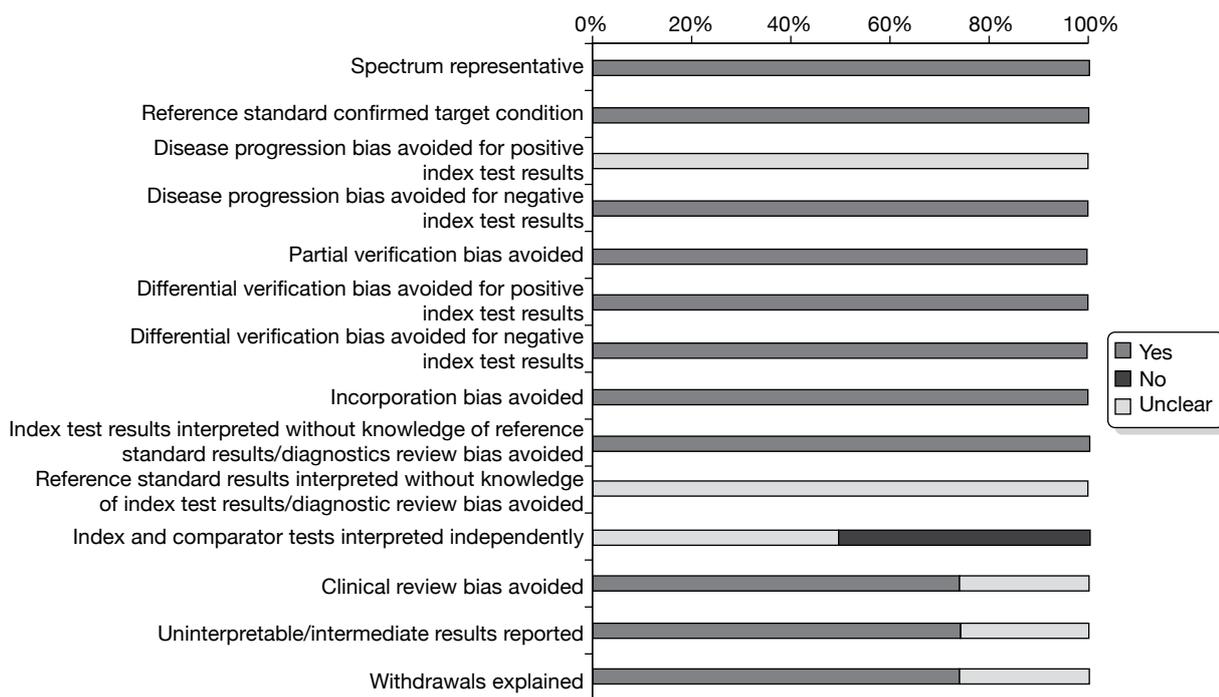
FIGURE 10 Summary of quality assessment of included diagnostic accuracy studies for non-routine surveillance.

avoided disease progression bias for positive index test results, whereas all studies successfully avoided disease progression bias for negative index test results.

Seven (78%) studies[64–66,68–70,72] (three routine surveillance and four non-routine surveillance) were free from partial verification bias. It was unclear in the study conducted by Shin and colleagues,[71] however, whether test negatives received follow-up. The study by Drew and colleagues[67] was considered to be vulnerable to partial verification bias, as only those participants testing positively on MRI received reference standard verification.

In all studies, positive index/comparator test results were verified by the same reference standard (histopathological assessment). In eight (89%) studies (four routine surveillance and four non-routine surveillance), participants with negative index/comparator test results all received follow-up.[64–70,72] In the study conducted by Shin and colleagues[71] it was unclear whether all patients with negative test results received follow-up.

While it was unclear for all studies whether reference standard results had been interpreted without knowledge of the index/comparator test result, it was unclear in the study by Viehweg and colleagues[70] whether index test results had been interpreted without knowledge of the reference standard. Five (56%) studies (three routine surveillance and two non-routine surveillance) interpreted index and comparator test results independently. It was unclear in the study by Boné and colleagues[64] whether index and comparator tests were interpreted independently. In the remaining studies,[65,69–72] index and comparator test results were not analysed separately. Clinical examination and mammography were usually performed before MRI or ultrasound. Knowledge of a prior test result could influence the subjective assessment, and hence the diagnostic accuracy performance, of the subsequent test(s).

In the study conducted by Rieber and colleagues[69] it was unclear whether the same clinical data were available as would be the case when the test is used in practice. It was also unclear

in the studies by Belli and colleagues[66] and Kim and colleagues[65] whether uninterpretable or intermediate results had been reported, and in the study conducted by Belli and colleagues[66] whether the number of or reason for withdrawals had been explained.

Assessment of test performance

Test performance in diagnosing IBTR

Table 17 shows test performance in detecting IBTR in routine surveillance patients. The studies by Boné and colleagues[64] and Drew and colleagues[67] involving a total of 188 patients reported the performance of surveillance mammography, MRI and clinical examination in routine surveillance patients. These studies reported sensitivities of 64% and 67%, and specificities of 97% and 85%, for surveillance mammography. For MRI the studies reported sensitivities of 86% and 100%, and 50% and 89% for clinical examination. Boné and colleagues[64] did not report specificity for MRI or clinical examination. The highest reported sensitivity was for MRI, and surveillance mammography combined with clinical examination (both 100%), whereas the highest specificity was for surveillance mammography (97%). Similarly, a high specificity of 93% was reported for MRI. The lowest reported sensitivity was for clinical examination (50%) and the lowest specificity was for surveillance mammography combined with clinical examination (67%).

Table 18 shows test performance in detecting IBTR in non-routine surveillance patients, as reported by Belli and colleagues,[66] Mumtaz and colleagues,[68] Rieber and colleagues[69] and Ternier and colleagues.[72] The studies by Boné and colleagues[64] and Drew and colleagues[67] involved a total of 156 patients and reported median (and range) sensitivity of 71% (50–83%) and specificity of 63% (57–75%) for surveillance mammography. For MRI, the studies by Belli and colleagues,[66] Mumtaz and colleagues[68] and Rieber and colleagues,[69] involving a total of 193 patients, reported sensitivity of 93% and 100% and a median (and range) specificity of 94% (88–96%). Belli and colleagues[66] and Ternier and colleagues[72] reported the test performance of ultrasound sensitivities of 43% and 87%, and specificities of 31% and 73%, and clinical examination, sensitivities of 43% and 62%, and specificities of 56% and 49%. The highest reported sensitivity (100%) and specificity (96%) were for MRI. The lowest reported sensitivities were for both ultrasound and clinical examination (43%). The lowest specificity was for ultrasound (31%).

TABLE 17 Test performance as measured by sensitivity, specificity, likelihood ratio and DOR for detecting IBTR in routine surveillance patients

Test	Study ID	Primary surgical treatment	Reported sensitivity (%)	Reported specificity (%)	LR+	LR–	DOR (95% CI)
XRM	Boné 1995[64]	Mastectomy	64	97	22.2	0.4	60.3 (10.2 to 358.1)
	Drew 1998[67]	Breast conserving	67	85	4.6	0.4	11.7 (2.6 to 52.4)
					1.9	0.5	4.2 (0.6 to 28.6)
MRI	Boné 1995[64]	Mastectomy	86	NR			
	Drew 1998[67]	Breast conserving	100	93	14.3	IC	IC
CE	Boné 1995[64]	Mastectomy	50	NR			
	Drew 1998[67]	Breast conserving	89	76	3.7	0.2	25.4 (3.0 to 213.9)
Combined XRM and CE	Drew 1998[67]	Breast conserving	100	67	3.0	IC	IC

CE, clinical examination; IC, incalculable; LR+, likelihood ratio of a positive test result; LR–, likelihood ratio of a negative test result; XRM, X-ray mammography.

TABLE 18 Test performance as measured by sensitivity, specificity, likelihood ratio and DOR for detecting IBTR in non-routine surveillance patients

Test	Study ID	Primary surgical treatment	Reported sensitivity (%)	Reported specificity (%)	LR+	LR–	DOR (95% CI)
XRM	Belli 2002[66]	Breast conserving	71	63	1.9	0.5	4.2 (2.6 to 52.4)
	Mumtaz 1997[68]		50	75	2.0	0.7	3 (0.6 to 14.0)
	Ternier 2006[72]		83	57	1.9	0.3	6.3 (2.5 to 15.6)
US	Belli 2002[66]		43	31	0.6	1.8	0.3 (0.1 to 2.1)
	Ternier 2006[72]		87	73	3.2	0.2	17 (6.2 to 46.5)
MRI	Belli 2002[66]		100	94	16.0	IC	IC
	Mumtaz 1997[68]		93	88	7.4	0.1	91 (7.4 to 1126. 9)
	Rieber 1997[69]		100	96	24.2	IC	IC
CE	Belli 2002[66]		43	56	1.0	1.0	1.0 (0.2 to 5.8)
	Ternier 2006[72]		62	49	1.2	0.8	1.5 (0.7 to 3.4)

CE, clinical examination; IC, incalculable; US, ultrasound; XRM, X-ray mammography.

Test performance in diagnosing MCBC

Table 19 shows test performance in detecting MCBC in routine surveillance patients. The studies by Boné and colleagues[64] and Viehweg and colleagues,[70] involving a total of 202 patients, reported 67% and 91% sensitivity and 50% and 90% specificity, respectively, for MRI. Only individual studies reported the test performance of surveillance mammography, clinical examination, and combinations of tests involving surveillance mammography. The highest reported sensitivity (100%) was for combined surveillance mammography, clinical examination, ultrasound and MRI,[70] whereas the highest reported specificity (99%) was for combined surveillance mammography and ultrasound.[65] The lowest reported sensitivity (0%) was for clinical examination and the lowest specificity was for surveillance mammography, MRI and clinical examination (all 50%).[64]

None of the studies reported diagnostic accuracy of the included tests for diagnosing MCBC in non-routine surveillance patients with a prior suspicious test result.

Test performance in diagnosing IBTR and MCBC

The study conducted by Shin and colleagues[71] was the sole study reporting overall test performance for diagnosing IBTR and MCBC. Shin and colleagues[71] evaluated ultrasound in routine surveillance patients, reporting a sensitivity of 71% and a specificity of 98% [LR+ 41.4, LR– 0.3, OR 138.25 (95% CI 61.26 to 312.04)].

Adverse effects, acceptability of the tests, reliability, radiological/operator expertise and interpretability/readability of the tests

None of the included studies reported data concerning these outcomes.

Histology of cancers detected and not detected (true-positives and false-negatives)

The histology of cancers detected and those that were not detected (true-positives and false-negatives), by each diagnostic test, where reported, are detailed in *Appendix 24* (see *Tables 60–63*). We found no discernible pattern for cancers detected and not detected both within and between diagnostic tests.

TABLE 19 Test performance as measured by sensitivity, specificity, likelihood ratio and DOR for detecting MCBC in routine surveillance patients

Test	Study ID	Primary surgical treatment	Reported sensitivity (%)	Reported specificity (%)	LR+	LR–	DOR (95% CI)
XRM	Boné 1995[64]	Mastectomy	67	50	1.3	0.7	2.0 (0.1 to 78.2)
MRI	Boné 1995[64]	Mastectomy	67	50	1.3	0.7	2.0 (0.1 to 78.2)
	Viehweg 2004[70]	Breast conserving	91	90	9.4	0.1	93.1 (11.0 to 786.2)
CE	Boné 1995[64]	Mastectomy	0	50			
Combined XRM and US	Kim 2009[65]	Mastectomy	95	99	61.5	0.05	1149.2 (148.0 to 8937.8)
Combined XRM, CE and US	Viehweg 2004[70]	Breast conserving	64	84	3.9	0.4	8.9 (2.4 to 33.0)
Combined XRM, CE, US and MRI	Viehweg 2004[70]	Breast conserving	100	89	8.9	IC	IC

CE, clinical examination; IC, incalculable; US, ultrasound; XRM, X-ray mammography.

Summary

Systematic reviews of diagnostic accuracy are highly complex and methodology in this area continues to evolve. We undertook a systematic review to determine the diagnostic accuracy of surveillance mammography for detecting IBTR and MCBC in women previously treated for primary breast cancer. We aimed to include RCT, head-to-head cohort and single cohort studies of women treated for primary breast cancer without detectable metastatic disease. The index test for our review was surveillance mammography and our comparator tests were ultrasound, MRI, specialist-led clinical examination and unstructured primary care follow-up. Our primary outcome was test performance in diagnosing IBTR and/or MCBC in routine and non-routine surveillance patients. The methods we adopted for this review are scientifically rigorous and compatible with current guidance in this area. Only nine studies, involving 3724 patients, evaluating the performance of tests for detecting IBTR and/or MCBC in women previously treated for primary breast cancer met our inclusion criteria. None of our considered tests was used for the same purpose (i.e. routine or non-routine surveillance) in all nine studies. Two studies evaluated the performance of surveillance mammography, and MRI, for detecting IBTR in routine surveillance patients. Three studies evaluated the performance of surveillance mammography, and MRI, for detecting IBTR in non-routine surveillance patients. None of the studies evaluated test performance for detecting MCBC in non-routine surveillance patients. *Table 20* summarises the sensitivities and specificities of the included studies. Results for the Boné and colleagues[64] study are excluded from this table due to the highly selected patient population of this study (mastectomy patients with breast reconstruction and implants).

For the detection of IBTR in routine surveillance patients with no prior suspicion of recurrence, the highest reported sensitivity was for MRI and surveillance mammography combined with clinical examination (both 100%), whereas the highest reported specificity was for surveillance mammography (97%) although it should be noted that this was reported for a highly select patient group (mastectomy patients with breast reconstruction and implants). The lowest reported sensitivity was for clinical examination (50%), whereas the lowest specificity (67%) was also for surveillance mammography combined with clinical examination. For the detection of IBTR in non-routine patients, with a suspicious result on a prior test, the highest reported sensitivity (100%) and specificity (96%) were for MRI. The lowest reported sensitivities were (43%) for both ultrasound and clinical examination each, whereas the lowest specificity was for ultrasound (31%).

TABLE 20 Summary of test performance in detecting IBTR and MCBC in routine surveillance and non-routine surveillance patients

Test	IBTR (routine surveillance)			IBTR (non-routine surveillance)			MCBC (routine surveillance)		
	No. of studies	Sensitivity (%)	Specificity (%)	No. of studies	Sensitivity (%)	Specificity (%)	No. of studies	Sensitivity (%)	Specificity (%)
XRM	2	64–67	85–97	3	(50–83)	(57–75)	1	67	50
US				2	(43–87)	(31–73)			
MRI	2	86–100	93	3	(93–100)	(88–96)	2	67–91	50–90
CE	2	50–89	76	2	(43–62)	(49–56)	1	0	50
Combined XRM, CE	1	100	67						
Combined XRM, US							1	95	99
Combined XRM, CE, US							1	64	84
Combined XRM, CE, US, MRI							1	100	89

CE, clinical examination; US, ultrasound; XRM, X-ray mammography.

For the detection of MCBC in routine surveillance patients, with no prior suspicion of contralateral cancer, the highest reported sensitivity (100%) was for a combination of surveillance mammography, clinical examination, ultrasound and MRI, whereas the highest reported specificity (99%) was for a combination of surveillance mammography and ultrasound. The lowest reported sensitivity (0%) was for clinical examination, with the lowest specificity for surveillance mammography, MRI and clinical examination (all 50%), although these results were reported for the highly selected patient group mentioned above. No study reported test performance for detecting MCBC in suspicious patients.

From the available data, MRI can be considered as a highly sensitive test for diagnosing IBTR in both routine surveillance and non-routine surveillance patients. In both routine and non-routine surveillance aimed at detecting IBTR, MRI[67–69] achieved higher reported specificities than surveillance mammography.[67,68,72] For the purposes of detecting routine surveillance MCBC, MRI[70] had the highest reported sensitivity and specificity of any other individual test. From the data presented, combining tests increases both sensitivity and specificity for detecting MCBC. Combining surveillance mammography, clinical examination, ultrasound and MRI[70] produced the highest reported sensitivity of 100%. This test combination produced a lower reported specificity of 89% compared with combining surveillance mammography and ultrasound,[65] which produced the highest reported specificity of 99% and the second highest reported sensitivity of 95%. Of those test combinations reported here, surveillance mammography combined with ultrasound could be considered as the most accurate test combination for detecting MCBC via routine surveillance. No data were available to assess test performance for the detection of non-routine surveillance MCBC.

These results should be interpreted with caution as they are based on a small evidence base of nine studies in total, with no one test evaluated by more than three studies, and most reported on by single studies only. Of the included studies, few have evaluated the performance of the considered tests for similar purposes. Due to differences between a 'treated' and 'untreated' breast (i.e. a breast that has undergone surgery and/or received radiotherapy) it is not appropriate to

compare test accuracy in detecting IBTR and MCBC. Similarly, it is inappropriate to compare test accuracy between routine and non-routine surveillance patients, as the test operator is primed to evaluate a suspicious finding in the non-routine surveillance patient. It is unclear what effect this has on test accuracy but it is likely to focus attention on a particular area of the breast and may arguably increase sensitivity. Given differences in breast density following treatment for primary breast cancer, we felt it would also be inappropriate to include studies of test performance in the screening population to make inferences for surveillance of the contralateral breast, although parameter estimates for MRI in the screening population have been used in the economic evaluation in *Chapter 7* of this report as it was felt that these would provide an indication of the relative value of a more costly but more effective test. Furthermore, no data were reported by the included studies on other test performance factors such as adverse effects or acceptability of the tests. We further discuss key findings and limitations of this review in *Chapter 8*.

Chapter 6

Analysis of Breast Cancer Registry database

Statement of overall aim and methods

The purpose of surveillance mammography is to try to allow the earliest possible diagnosis of breast cancer and hence assume the tumour size at diagnosis is reduced. In order to ascertain the effectiveness of surveillance mammography we tried to identify a database with information on mammographic detection of IBTR and MCBC. Despite contacting a number of clinical and research groups and searching several databases, we were unable to locate a suitable data set with the required information. Furthermore, there was no information on how the IBTR or MCBC had been detected or on the follow-up mammography regimen of women diagnosed with breast cancer in any of the databases to which we had access. We required a representative UK cohort on which to base assumptions for our economic model (reported in *Chapter 7*). We also required a data set with a large number of IBTR and MCBC in a contemporary cohort with detailed information about the primary tumour to determine whether IBTR or MCBC constituted an independent risk of death. In the absence of mammography information, we wanted to determine whether size of the IBTR or MCBC was an independent risk factor for death, because if this is not the case then surveillance mammography is irrelevant.

We undertook an analysis of the West Midlands Cancer Intelligence Unit (WMCIU) breast cancer database to assess the generalisability of this database to UK breast cancer patients, to confirm risk factors for IBTR and MCBC, to determine if IBTR and MCBC were risk factors for all-cause death and breast cancer death, and to determine whether the size of the subsequent breast cancer tumour was a risk factor for death, given the risk factors of the primary tumour. If it was demonstrated that women who had an IBTR or MCBC were at an increased risk of death and that the size of the second tumour was associated with an elevated risk of death then it could be inferred that surveillance mammography may be an effective way to detect these second tumours and improve prognosis in breast cancer survivors.

The WMCIU breast cancer primary tumour cohorts

The WMCIU database contained information on 68,677 tumours in women diagnosed with breast cancer from 1 January 1990 to 31 December 2007. Follow-up data were available up until 31 January 2009. Tumours were excluded from analysis if the primary cancer was non-invasive or the treatment did not include surgical management in order to be able to distinguish future occurrences of ipsilateral local recurrence from progressive disease (*Figure 11*). Further exclusions were made if there was no information on risk factors recorded or if date of death was the same as the date of diagnosis. In the event of multiple primary tumours in the same breast or bilateral tumours, the worst tumour, as defined by the Nottingham Prognostic Index, was used.[73] Prior to 1997 the WMCIU did not routinely collect information on all of the risk factors included in the analyses. For example, since 1997 the number of involved lymph nodes has been collected in addition to nodal status (positive or negative), which had not been collected prior to this date. Because of this, we took the pragmatic decision to include tumours diagnosed only after 1 January 1997 in the analyses. After exclusions, there were 32,877 women
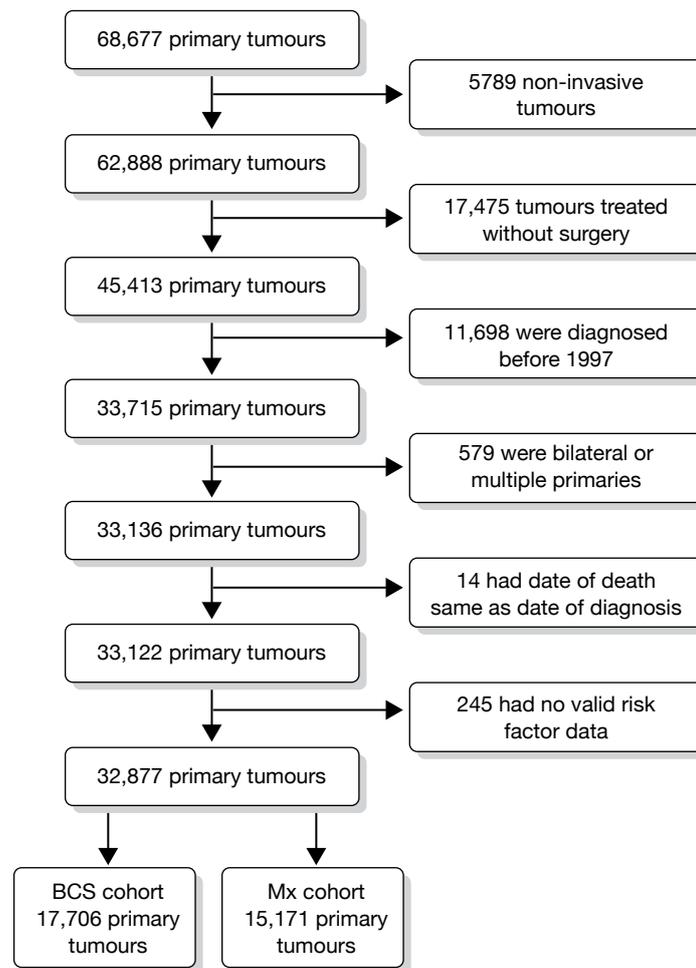
FIGURE 11 Flow chart of exclusion of primary tumours. Mx, mastectomy cohort.

with tumour data available for analysis. This total was split into two primary tumour cohorts to be analysed separately based on the type of surgery received: the BCS cohort of 17,706 women and the mastectomy cohort of 15,171 women. Descriptive information on both of the cohorts is contained in *Table 21*.

Methods

In both cohorts of primary tumours, Cox proportional hazards regression models[74,75] were used to model four outcomes: time to IBTR, time to MCBC, time to death from all causes, and time to death from breast cancer. All risk factors were explored univariately in a simple Cox regression model and then simultaneously in a multiple Cox regression model. Risk factors modelled were age at diagnosis (≤ 34, 35–49, 50–64, 65–74, 75–79, ≥ 80 years); grade of primary tumour (grade 1, grade 2, grade 3, grade unknown); size of primary tumour (≤ 10 mm, > 10 mm to < 20 mm, ≥ 20 mm, size unknown); nodal status (no nodes involved, one to three nodes involved, four or more nodes involved, nodal status unknown); and vascular invasion (no, yes, unknown). For all risk factors the level of the factor with the best prognosis was used as the reference category, with the exception of age at diagnosis where the screening age group (50–64 years of age) was used as the reference category. If a woman was indicated as having both an IBTR and MCBC then whichever event was detected earliest defined the event for that particular woman. Any IBTR or MCBC that occurred within 6 months of diagnosis was excluded, as this might be identified as

TABLE 21 Description of the primary tumour cohorts

	BCS (*n* = 17,706)		Mastectomy (*n* = 15,171)		Total (*n* = 32,877)	
Outcomes						
Death all cause	2528		4345		6873	
Death breast cancer	1378		2713		4091	
Ipsilateral event	455		310		765	
Contralateral event	260		262		522	
Age at diagnosis (years)						
Mean (SD)	59 (12)		61 (14)		60 (13)	
Median (25th, 75th centile)	58 (50, 67)		61 (50, 72)		59 (50, 69)	
Minimum, maximum	20, 99		20, 97		20, 99	
	n	*%*	*n*	*%*	*n*	*%*
Age categories (years)						
≤ 34	350	2.0	360	2.4	710	2.2
35–49	3513	19.8	3188	21.0	6701	20.4
50–64	8511	48.1	5229	34.5	13,740	41.8
65–74	3491	19.7	3422	22.6	6913	21.0
75–79	1034	5.8	1547	10.2	2581	7.9
80+	807	4.6	1425	9.4	2232	6.8
Grade						
1	4193	23.7	1827	12.0	6020	18.3
2	7697	43.5	6918	45.6	14,615	44.5
3	5388	30.4	5852	38.6	11,240	34.2
Unknown	428	2.4	574	3.8	1002	3.0
Size (mm)						
≤ 10	3473	19.6	1103	7.3	4576	13.9
> 10 to < 20	8663	48.9	4224	27.8	12,887	39.2
≥ 20	4885	27.6	8627	56.9	13,512	41.1
Size cat. unknown	685	3.9	1217	8.0	1902	5.8
Nodes						
0	11,630	65.7	6938	45.7	18,568	56.5
1–3	3367	19.0	4147	27.3	7514	22.9
4+	1232	7.0	3402	22.4	4634	14.1
Unknown	1477	8.3	684	4.5	2161	6.6
Vascular invasion						
No	12,887	72.8	8608	56.7	21,495	65.4
Yes	3559	20.1	5341	35.2	8900	27.1
Unknown	1260	7.1	1222	8.1	2482	7.5

part of the management of the primary tumour and therefore would not be identifiable as part of a surveillance regimen.

Ipsilateral breast tumour recurrence (no, yes) and MCBC (no, yes) were entered into the multiple Cox regression for modelling death from all causes and death from breast cancer. HRs and 95% CIs are presented. Complete tables of the univariate Cox regression models are reported in

Appendix 25, summary tables of the multiple regression models are below. Kaplan–Meier[76] failure curves are presented for selected risk factors and outcomes. Incidence rates were plotted against time for both IBTR and MCBC in both primary tumour cohorts.

Results

There were 32,877 women with primary breast cancer who met the inclusion criteria for analysis (see *Table 21*). These cohorts were younger on average than the total population of women diagnosed with breast cancer. This is because we excluded all women who were not treated with a surgical option and these tended to be older women. The BCS cohort consisted of 90,171 years of follow-up and the women had a median follow-up of 5 years. There were 73,500 years of follow-up in the mastectomy cohort and median follow-up was 4 years.

Incidence of recurrences

Incidence rates per 1000 persons are plotted against year of follow-up in *Figures 12* and *13*.
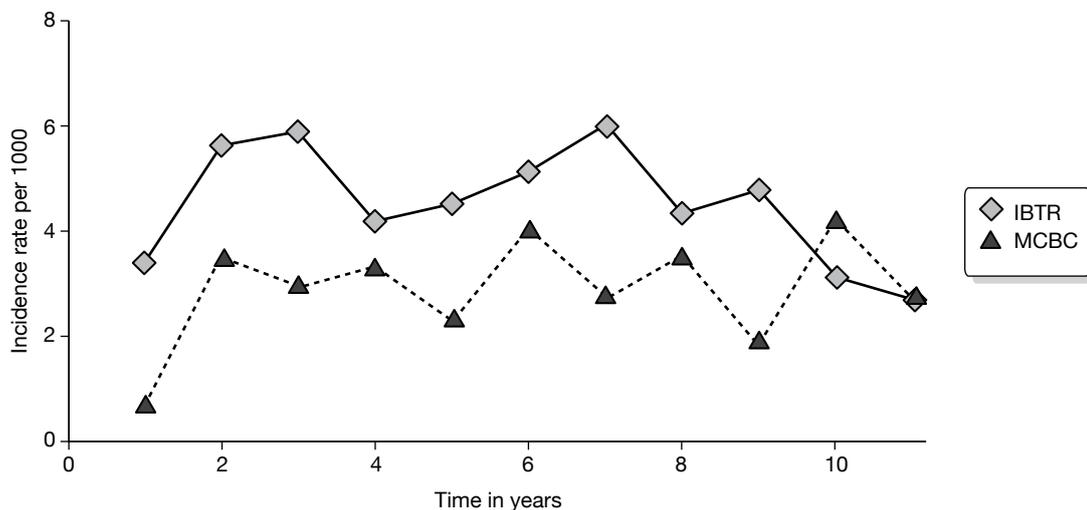
FIGURE 12 Incidence per 1000 per year of IBTR and MCBC occurrence for BCS cohort.
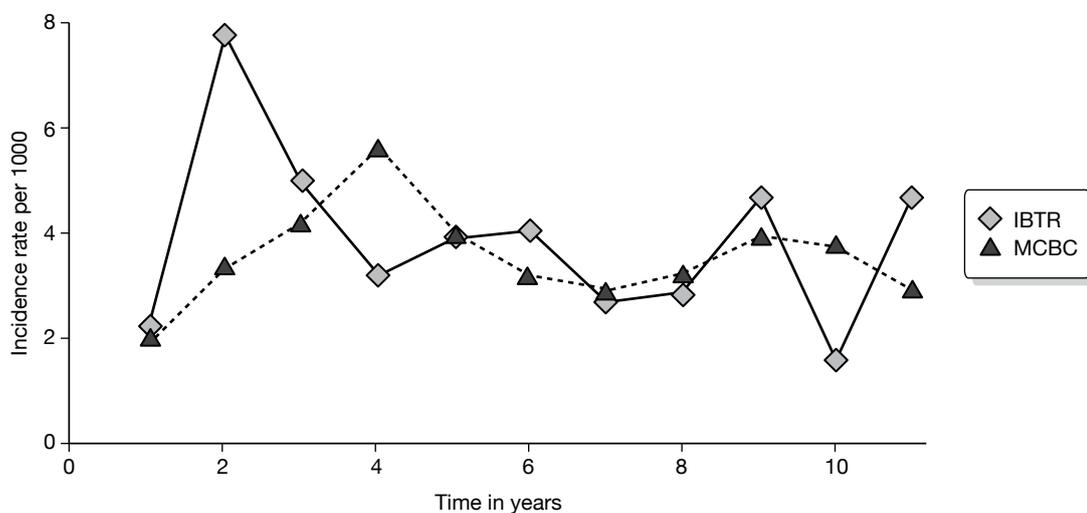
FIGURE 13 Incidence per 1000 per year of IBTR and MCBC occurrence for mastectomy cohort.

Breast-conserving surgery cohort

Estimates from Cox proportional hazards regression models for time to outcome (IBTR, MCBC, death from all causes and death from breast cancer) in the BCS cohort are shown in *Table 22*. Tables with details of the univariate regression models are included in *Appendix 25*.

All risk factors were univariately associated with an increased hazard of IBTR. In particular, age ≤ 34 years, grade 3 tumour, large tumour (≥ 20 mm), nodal involvement (four or more nodes) and vascular invasion (yes) all had HRs of approximately two or above (*Appendix 25*, *Table 64*). In the multiple Cox regression model (*Table 22*) the estimates were broadly consistent with the univariate models. Grade 3 tumour, age ≤ 34 and nodal involvement (four or more nodes) in particular were associated with elevated risk of IBTR.

Univariately there was little that was associated with an increased risk of MCBC in the BCS group of women (*Appendix 25*, *Table 65*). Older women were at a reduced risk of MCBC. Women with a primary tumour ≥ 20 mm were at an increased risk of MCBC, HR 1.60 (95% CI 1.08 to 2.38).

The Kaplan–Meier failure curves in *Figure 14* show that women who experienced IBTR were at an increased risk of death from all causes. All risk factors were associated univariately with an increased risk of all-cause death although there was no evidence that the group aged 35–49 years was different in terms of all-cause mortality to the reference group (*Appendix 25*, *Table 66*). In the multiple Cox regression model (*Table 22)* all of the risk factors were associated with an increased risk of death, but the youngest age group (age ≤ 34 years) was no longer different from the reference group. IBTR was a risk factor, which was associated with an increased risk of death univariately, HR 2.29 (95% CI 1.97 to 2.67). In the multiple Cox regression model, adding IBTR was still associated with an increased risk of death, HR 1.76 (95% CI 1.51 to 2.05). There was no evidence that MCBC was related to an elevated risk of death in the BCS cohort, HR 1.05 (95% CI 0.80 to 1.39) (see *Figure 14*).

All risk factors were associated univariately with an increased risk of death from breast cancer (*Appendix 25*, *Table 67*). In particular, the worst prognostic categories of each risk factor were associated with an increased risk of death from breast cancer. IBTR was also associated with an increased risk of death from breast cancer (*Figure 15*). MCBC was excluded from the models as a risk factor as there were only three cases out of 260 MCBC cases that were coded as having died from breast cancer. In the multiple Cox regression model (*Table 22*) there was no evidence that the age groups younger than the reference group were different in terms of risk of death from breast cancer. The remaining risk factors were associated with an increased risk of death from breast cancer and after adjusting for the other risk factors IBTR was an independent predictor, HR 2.13 (95% CI 1.78 to 2.56).

Mastectomy cohort

Estimates from Cox proportional hazards regression models for time to outcome (IBTR, MCBC, death from all causes and death from breast cancer) in the mastectomy cohort are shown in *Table 23*. Tables with details of the univariate regression models are included in *Appendix 25*.

Univariately the worst prognosis levels of the risk factors were associated with an increased risk of IBTR in women treated with mastectomy (*Appendix 25*, *Table 68*). In the multiple Cox regression model the increased risk was associated with grade 3 primary tumour, nodal involvement (four or more nodes) and vascular invasion (yes).

Univariately the worst levels of risk factors were associated with an increased risk of MCBC in cases treated with mastectomy (*Appendix 25*, *Table 69*). In the multiple Cox regression model, older women were at reduced risk of contralateral tumour, adjusting for other risk factors

TABLE 22 Cox proportional hazard regression models for time to outcome in the BCS cohort

	IBTR			MCBC			All-cause death			Breast cancer death		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)												
≤34	2.28	1.51 to 3.47	<0.001	1.54	0.82 to 2.86	0.177	1.00	0.77 to 1.30	0.987	1.21	0.91 to 1.60	0.182
35–49	1.44	1.15 to 1.80	0.002	0.85	0.62 to 1.16	0.294	0.78	0.69 to 0.89	<0.001	0.90	0.78 to 1.04	0.157
50–64	(1.0)			(1.0)			(1.0)			(1.0)		
65–74	0.72	0.53 to 0.97	0.033	0.61	0.42 to 0.89	0.010	1.80	1.62 to 2.01	<0.001	1.28	1.1 to 1.48	0.001
75–79	0.96	0.63 to 1.47	0.852	0.34	0.15 to 0.77	0.010	2.55	2.23 to 2.93	<0.001	1.27	1.02 to 1.58	0.034
80+	1.28	0.81 to 2.03	0.289	0.46	0.18 to 1.14	0.093	4.83	4.22 to 5.52	<0.001	2.06	1.65 to 2.57	<0.001
Grade												
1	(1.0)			(1.0)			(1.0)			(1.0)		
2	1.53	1.14 to 2.07	0.005	0.92	0.68 to 1.26	0.623	1.33	1.17 to 1.50	<0.001	2.60	2.03 to 3.32	<0.001
3	2.32	1.71 to 3.16	<0.001	1.06	0.75 to 1.49	0.756	2.20	1.93 to 2.50	<0.001	5.31	4.17 to 6.77	<0.001
Unknown	1.85	1.06 to 3.26	0.032	1.40	0.71 to 2.76	0.329	1.15	0.88 to 1.50	0.207	2.39	1.62 to 3.54	0.207
Size (mm)												
≤10	(1.0)			(1.0)			(1.0)			(1.0)		
>10 to <20	0.81	0.61 to 1.09	0.161	1.25	0.88 to 1.76	0.217	1.32	1.14 to 1.53	<0.001	1.73	1.35 to 2.21	<0.001
≥20	1.31	0.97 to 1.78	0.078	1.60	1.08 to 2.38	0.019	2.04	1.76 to 2.37	<0.001	3.04	2.37 to 3.89	<0.001
Size cat. unknown	1.28	0.83 to 1.96	0.268	1.81	1.01 to 3.22	0.044	1.54	1.25 to 1.91	<0.001	2.09	1.52 to 2.88	<0.001

	IBTR			MCBC			All-cause death			Breast cancer death		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Nodes												
0	(1.0)			(1.0)			(1.0)			(1.0)		
1–3	1.33	1.04 to 1.69	0.021	0.72	0.50 to 1.03	0.075	1.57	1.41 to 1.74	<0.001	1.82	1.59 to 2.10	<0.001
4+	2.04	1.51 to 2.77	<0.001	1.20	0.73 to 1.96	0.479	2.96	2.62 to 3.34	<0.001	3.88	3.34 to 4.51	<0.001
Unknown	2.06	1.51 to 2.81	<0.001	1.07	0.67 to 1.73	0.771	1.92	1.70 to 2.17	<0.001	2.23	1.85 to 2.69	<0.001
Vascular invasion												
No	(1.0)			(1.0)			(1.0)			(1.0)		
Yes	1.26	1.01 to 1.57	0.043	0.74	0.52 to 1.05	0.096	1.36	1.24 to 1.49	<0.001	1.59	1.41 to 1.79	<0.001
Unknown	0.98	0.68 to 1.41	0.928	0.58	0.33 to 1.01	0.053	1.15	0.99 to 1.33	0.066	1.09	0.88 to 1.36	0.430
Ipsilateral recurrence												
No												
Yes							1.76	1.51 to 2.05	<0.001	2.13	1.78 to 2.56	<0.001
Contralateral occurrence												
No							(1.00)					
Yes							1.05	0.80 to 1.39	0.715			
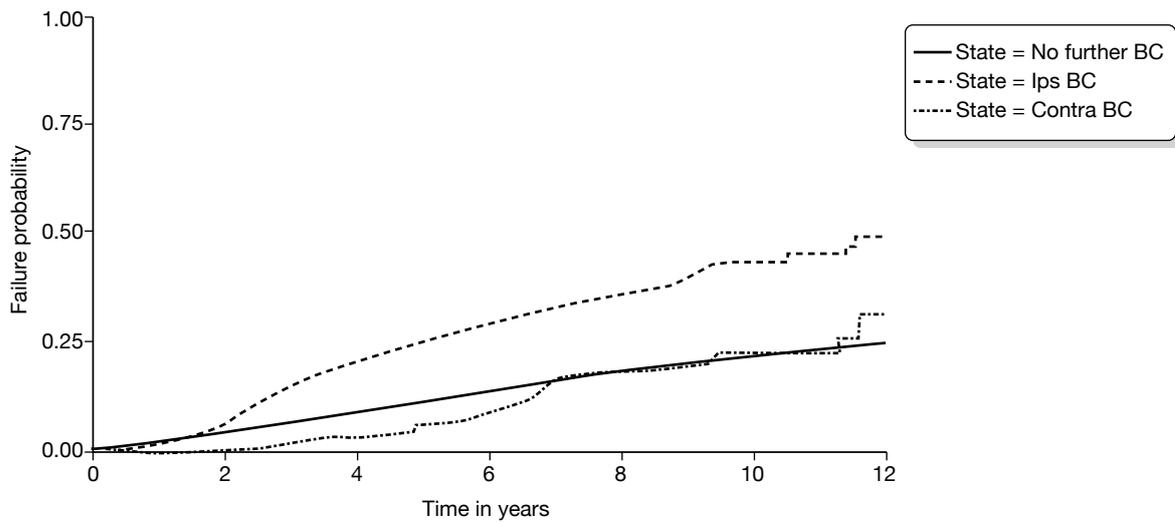
FIGURE 14 Kaplan–Meier failure curves for BCS cohort for time to death from all causes by disease status. BC, breast cancer.
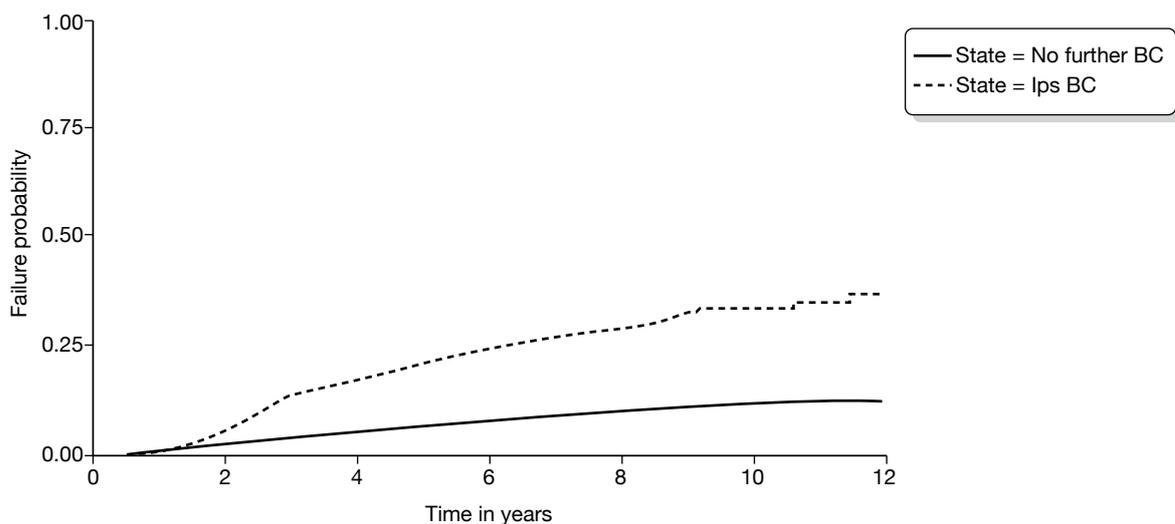
FIGURE 15 Kaplan–Meier failure curves for BCS cohort for time to death from breast cancer by disease status. BC, breast cancer.

(compared to the reference screening age group). Tumour size (≥ 20 mm) and nodal involvement (four or more nodes) were associated with an increased risk of MCBC.

All risk factors were associated univariately with increased risk of all-cause death, although there was evidence that risk of death from all causes in the 35- to 49-year age group of women was slightly reduced (*Appendix 25*, *Table 70*). In the multiple Cox regression model all the risk factors were associated with an increased risk of death, but the youngest age group (≤ 34 years) had a similar risk of all-cause death as that of the reference age group. IBTR was a risk factor for death from all causes in a univariate analysis, HR 2.14 (95% CI 1.86 to 2.47), but MCBC was not, HR 1.01 (95% CI 0.83 to 1.24) (*Figure 16*). The estimates of the HRs for all risk factors from the univariate model were attenuated slightly in the multiple Cox model and IBTR was still associated with increased risk of death. However, a contralateral recurrence was not associated with an elevated risk of all-cause death in the mastectomy cohort.

TABLE 23 Cox proportional hazard regression models for time to outcome in the mastectomy cohort

	IBTR			MCBC			All-cause death			Breast cancer death		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)												
≤34	0.97	0.51 to 1.87	0.937	1.55	0.87 to 2.77	0.138	0.99	0.81 to 1.20	0.895	1.08	0.87 to 1.33	0.477
35–49	0.85	0.62 to 1.16	0.298	0.89	0.65 to 1.21	0.459	0.78	0.71 to 0.86	<0.001	0.85	0.76 to 0.94	0.002
50–64	(1.0)			(1.0)			(1.0)			(1.0)		
65–74	1.14	0.85 to 1.54	0.368	0.77	0.55 to 1.07	0.118	1.54	1.42 to 1.68	<0.001	1.17	1.06 to 1.30	0.002
75–79	0.97	0.63 to 1.49	0.882	0.45	0.25 to 0.81	0.007	2.18	1.98 to 2.41	<0.001	1.26	1.10 to 1.44	0.002
80+	0.98	0.62 to 1.57	0.945	0.27	0.12 to 0.61	0.002	3.29	2.99 to 3.61	<0.001	1.51	1.31 to 1.74	0.001
Grade												
1	(1.0)			(1.0)			(1.0)			(1.0)		
2	1.23	0.78 to 1.94	0.363	0.91	0.61 to 1.37	0.660	1.21	1.08 to 1.36	0.001	1.68	1.38 to 2.04	<0.001
3	2.06	1.31 to 3.24	0.002	1.18	0.78 to 1.79	0.436	2.02	1.79 to 2.27	<0.001	3.38	2.79 to 4.10	<0.001
Unknown	1.44	0.73 to 2.82	0.293	0.87	0.41 to 1.86	0.726	1.35	1.13 to 1.61	0.001	1.9	1.43 to 2.51	<0.001
Size (mm)												
≤10	(1.0)			(1.0)			(1.0)			(1.0)		
>10 to <20	1.24	0.68 to 2.25	0.485	1.45	0.78 to 2.69	0.244	1.38	1.14 to 1.66	0.001	1.74	1.29 to 2.34	<0.001
≥20	1.43	0.8 to 2.56	0.224	1.81	0.99 to 3.31	0.054	2.02	1.68 to 2.42	<0.001	2.83	2.12 to 3.77	<0.001
Size cat. unknown	2.61	1.40 to 4.84	0.002	1.74	0.87 to 3.50	0.117	2.1	1.72 to 2.56	<0.001	3.08	2.27 to 4.18	<0.001

TABLE 23 Cox proportional hazard regression models for time to outcome in the mastectomy cohort *(continued)*

	IBTR			MCBC			All-cause death			Breast cancer death		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Nodes												
0	(1.0)			(1.0)			(1.0)			(1.0)		
1–3	0.95	0.69 to 1.29	0.723	0.95	0.69 to 1.31	0.774	1.5	1.38 to 1.63	<0.001	1.92	1.71 to 2.15	<0.001
4+	1.62	1.20 to 2.19	0.002	1.53	1.10 to 2.12	0.012	2.7	2.49 to 2.92	<0.001	3.89	3.49 to 4.34	<0.001
Unknown	2.55	1.65 to 3.95	<0.001	1.44	0.76 to 2.75	0.264	2.45	2.16 to 2.77	<0.001	2.96	2.47 to 3.54	<0.001
Vascular invasion												
No	(1.0)			(1.0)			(1.0)			(1.0)		
Yes	1.68	1.29 to 2.19	<0.001	1.09	0.82 to 1.45	0.543	1.37	1.28 to 1.47	<0.001	1.51	1.38 to 1.65	<0.001
Unknown	1.25	0.82 to 1.90	0.307	0.89	0.53 to 1.50	0.669	1.14	1.01 to 1.28	0.03	1.28	1.10 to 1.49	0.002
Ipsilateral recurrence												
No							(1.0)			(1.0)		
Yes							1.64	1.42 to 1.89	<0.001	2.12	1.80 to 2.50	<0.001
Contralateral occurrence												
No							(1.0)					
Yes							0.99	0.81 to 1.21	0.906			

All risk factors were associated univariately with an increased risk of breast cancer death although there was no evidence that the group aged 35–49 years were different in terms of risk of death from breast cancer compared with the reference group (*Appendix 25*, *Table 71*). IBTR was a risk factor which was associated with an increased risk of death from breast cancer, HR 2.78 (95% CI 2.37 to 3.27) (*Figure 17*). In the multiple Cox regression model (*Table 23*) all of the risk factors were associated with an increased risk of death, but in the youngest age group (age ≤ 34 years) the risk of death from breast cancer was reduced. There was no evidence that, after correcting for other risk factors, this age group is at a different risk of death from breast cancer compared with the reference group. In the multiple Cox regression model IBTR was still associated with an increased risk of death from breast cancer, HR 2.12 (95% CI 1.80 to 2.50). This indicates that an IBTR was related to an increased risk of death from breast cancer even after adjusting for all the other risk factors. MCBC was excluded from the models as a risk factor, as there were only six out of 262 MCBC cases that were coded as having died from breast cancer.
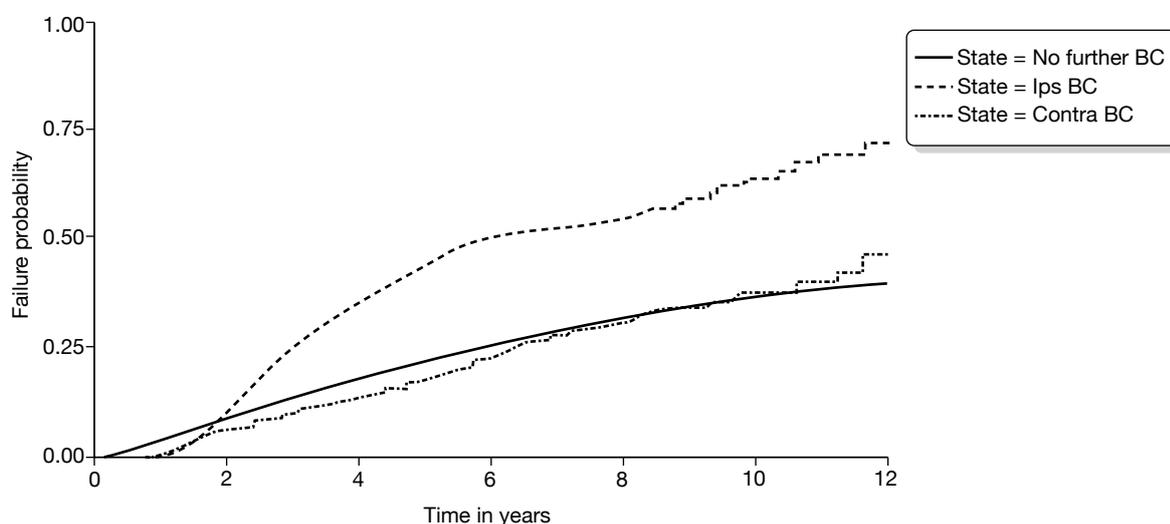

FIGURE 16 Kaplan–Meier failure curves for mastectomy cohort for time to death from all causes by disease status. BC, breast cancer.
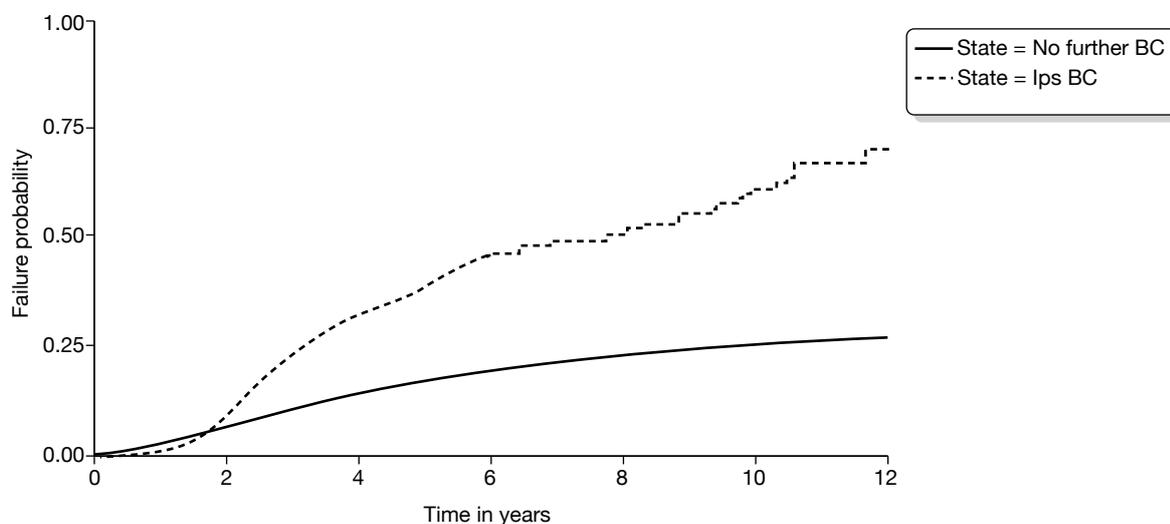

FIGURE 17 Kaplan–Meier failure curves for mastectomy cohort for time to death from breast cancer by disease status. BC, breast cancer.

WMCIU second tumour cohorts

The WMCIU database contained information on 2045 ipsilateral tumours and 1355 contralateral tumours, defined as 'second' tumours, in women diagnosed with breast cancer from 1 January 1990 to 31 January 2007. Second tumours were excluded from our analysis if the primary tumour could not be identified or management of the primary tumour did not include a surgical treatment (*Figures 18* and *19*). A further exclusion category was a non-invasive primary tumour. However, after exclusion on the previous criteria there were no women remaining who had experienced a non-invasive primary tumour. Further exclusions were made if there was no information on risk factors recorded or if date of death was the same as the date of diagnosis. In the event of multiple second tumours in the same breast, or in the contralateral breast, the tumour with the worst prognosis as defined by the Nottingham Prognostic Index was used.[73] Descriptive information on both these cohorts of women is contained in *Tables 24* and *25*.

Methods

We modelled the following risk factors relating to characteristics of the primary tumour: age at diagnosis (≤ 34, 35 to 49, 50–64, 65–74, 75 to 79, ≥ 80 years), grade of primary tumour (grade 1, grade 2, grade 3, grade unknown), size of primary tumour (≤ 10 mm, > 10 mm to < 20mm, ≥ 20mm, size unknown), nodal status (no nodes involved, one to three nodes involved, four or more nodes involved, nodal status unknown), vascular invasion (no, yes, unknown), and type of surgery (BCS or mastectomy). Modelled risk factors associated with the second tumour were time to second tumour (< 60 months or ≥ 60 months) and size of second tumour (≤ 10 mm, > 10 mm to < 20 mm, ≥ 20 mm, size unknown). For all categorical risk factors the level of the factor with best prognosis was used as the reference category, with the exception of age at diagnosis where the screening age group (50–64 years of age) was used as the reference category.
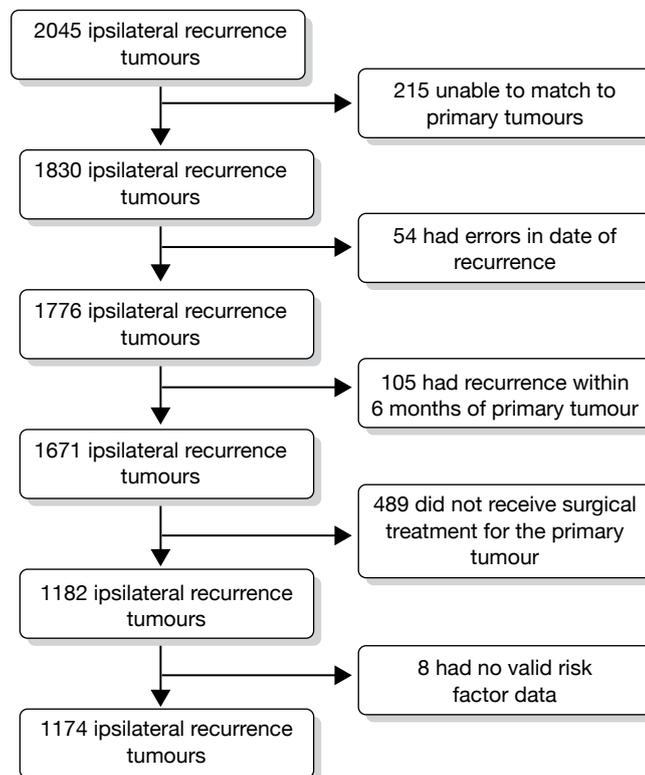
FIGURE 18 Flow chart of ipsilateral recurrence tumours (IBTR).
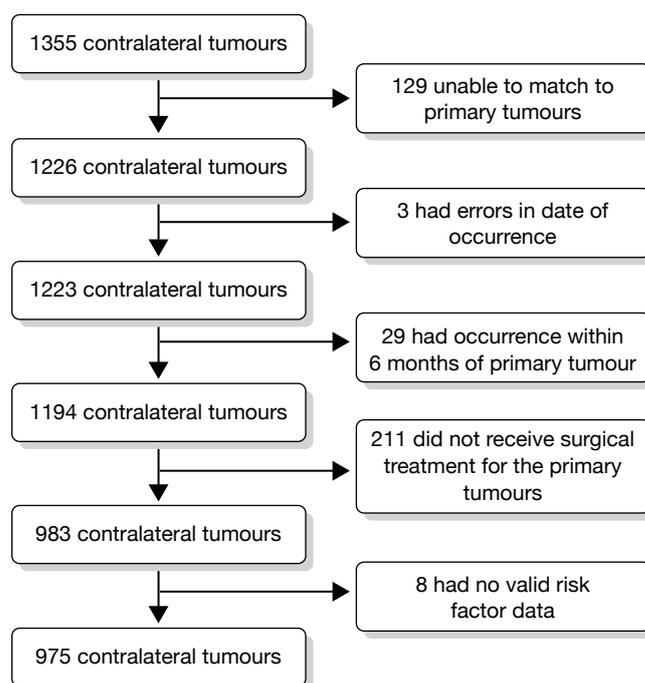
FIGURE 19 Flow chart of contralateral tumours.

TABLE 24 Description of the IBTR cohort

	Received BCS: 739 (62.9%)		Received mastectomy: 435 (37.1%)		Total: 1174	
Death all cause	322		291		613	
Death breast cancer	219		223		442	
Age at diagnosis of primary tumour (years)						
Mean (SD)	55 (13)		59 (13)		57 (14)	
Median (25th, 75th centile)	53 (45, 63)		58 (49, 70)		55 (47, 67)	
Minimum, maximum	20, 88		24, 93		20, 93	
	n	%	*n*	%	*n*	%
Age categories (years)						
≤ 34	41	5.5	13	3.0	54	4.6
35–49	227	30.7	97	22.3	324	27.6
50–64	295	39.9	158	36.3	453	38.6
65–74	100	13.5	99	22.8	199	17.0
75–79	42	5.7	42	9.7	84	7.2
80+	34	4.6	26	6.0	60	5.1
Grade						
1	108	14.6	30	6.9	138	11.8
2	270	36.5	178	40.9	448	38.2
3	282	38.2	188	43.2	470	40.0
Unknown	79	10.7	39	9.0	118	10.1

TABLE 24 Description of the IBTR cohort *(continued)*

	Received BCS: 739 (62.9%)		Received mastectomy: 435 (37.1%)		Total: 1174	
Size (mm)						
≤ 10	111	15.0	13	3.0	124	10.6
> 10 to < 20	287	38.8	91	20.9	378	32.2
≥ 20	247	33.4	244	56.1	491	41.8
Size unknown	94	12.7	87	20.0	181	15.4
Nodes						
0	333	45.1	150	34.5	483	41.1
1–3	139	18.8	96	22.1	235	20.0
4+	72	9.7	126	29.0	198	16.9
Unknown	195	26.4	63	14.5	258	22.0
Vascular invasion						
No	376	50.9	152	34.9	528	45.0
Yes	194	26.3	193	44.4	387	33.0
Unknown	169	22.9	90	20.7	259	22.1
Time to second tumour (months)						
Median (25th, 75th centile)	45	22, 83	34	18, 64	21	40.76
< 60	447	60.5	309	71.0	756	64.4
Size of recurrence						
≤ 10	140	18.9	51	11.7	191	16.3
> 10 to < 20	199	26.9	61	14.0	260	22.1
≥ 20	190	25.7	62	14.3	252	21.5
Size unknown	210	28.4	261	60.0	471	40.1

We undertook a multiple Cox regression model that included the risk factors associated with the primary tumour, time to the second tumour event and the size of second tumour. Outcomes for these models were time to death from all causes and time to death from breast cancer.

Results

There were 1174 women with 3870 years of follow-up in the IBTR cohort, of whom there were 613 deaths from all causes and 442 deaths from breast cancer. Median time from diagnosis of primary tumour to diagnosis of second tumour was 21 months.

Estimates from Cox regression models for time to death from all causes in the IBTR cohort are shown in *Table 26*. Women with a second tumour of ≥ 20 mm in maximum diameter were at an elevated risk of death compared with the reference group of ≤ 10 mm, HR 1.75 (95% CI 1.29 to 2.37). This was also evident from the Kaplan–Meier failure curves in *Figure 20*.

Estimates from Cox regression models for time to death from breast cancer in the IBTR cohort are shown in *Table 26*. Women with a second tumour of ≥ 20 mm were at an elevated risk of death compared with the reference group of ≤ 10 mm, HR 1.99 (95% CI 1.37 to 2.89). This was also evident from the Kaplan–Meier failure curves in *Figure 21*.

TABLE 25 Description of the MCBC occurrence cohort

	Received BCS: 534 (54.8%)		Received mastectomy: 441 (45.2%)		Total: 975	
Death all cause	158		200		358	
Death breast cancer	11		12		23	
Age at diagnosis of primary tumour (years)						
Mean (SD)	55 (11)		56 (12)		55 (12)	
Median (25th, 75th centile)	55 (47, 62)		55 (47, 65)		55 (47, 63)	
Minimum, maximum	25, 86		26, 86		25, 86	
	n	*%*	*n*	*%*	*n*	*%*
Age categories (years)						
≤ 34	27	5.1	18	41	45	4.6
35–49	141	26.4	122	27.7	263	27.0
50–64	278	52.1	188	42.6	466	47.8
65–74	65	12.2	80	18.1	145	14.9
75–79	17	3.2	24	5.4	41	4.2
80+	6	1.1	9	2.0	15	1.5
Grade						
1	113	21.2	47	10.7	160	16.4
2	199	37.3	165	37.4	364	37.3
3	150	28.1	167	37.9	317	32.5
Unknown	72	13.5	62	14.1	134	13.7
Size (mm)						
≤ 10	84	15.7	22	5.0	106	10.9
> 10 to < 20	249	46.6	106	24.0	355	36.4
≥ 20	133	24.9	241	54.6	374	38.4
Size unknown	68	12.7	72	16.3	140	14.4
Nodes						
0	298	55.8	187	42.4	485	49.7
1–3	74	13.9	103	23.4	177	18.2
4+	24	4.5	106	24.0	130	13.3
Unknown	138	25.8	45	10.2	183	18.8
Vascular invasion						
No	288	53.9	187	42.4	475	48.7
Yes	80	15.0	144	32.7	224	23.0
Unknown	166	31.1	110	24.9	276	28.3
Time to second tumour (months)						
Median (25th, 75th centile)	60	33, 95	44	26, 79	52	29, 88
< 60	261	49.0	281	63.4	542	55.6
Size of recurrence (mm)						
≤ 10	119	22.3	86	19.5	205	21.0
> 10 to < 20	185	36.6	124	28.1	309	31.7
≥ 20	135	25.3	119	27.0	254	26.1
Size unknown	95	17.8	112	25.4	207	21.2
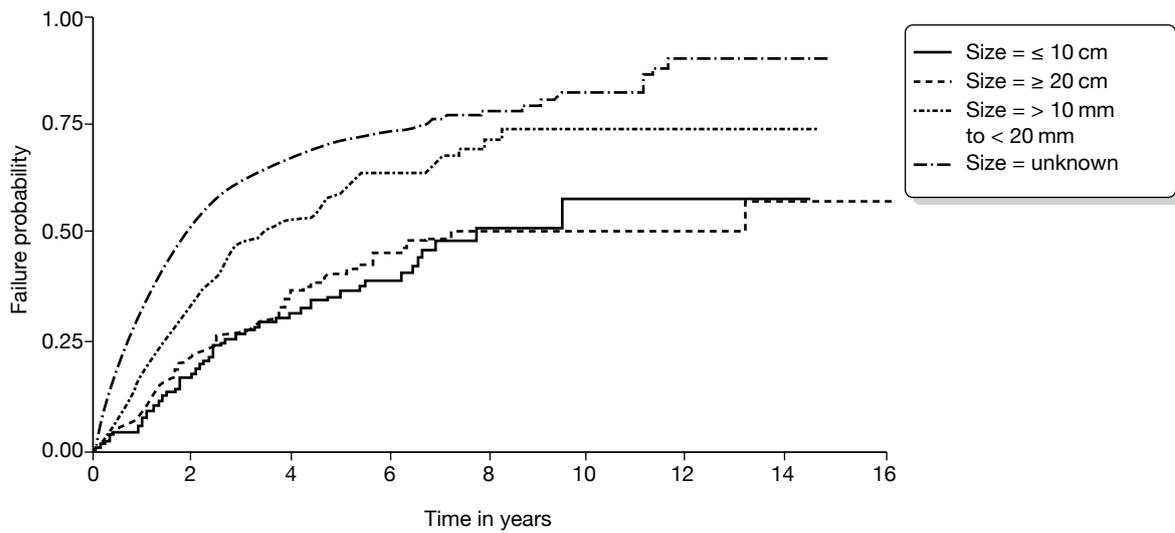
FIGURE 20 Kaplan–Meier failure curves for IBTR cohort for time to death from all causes by size of second tumour.
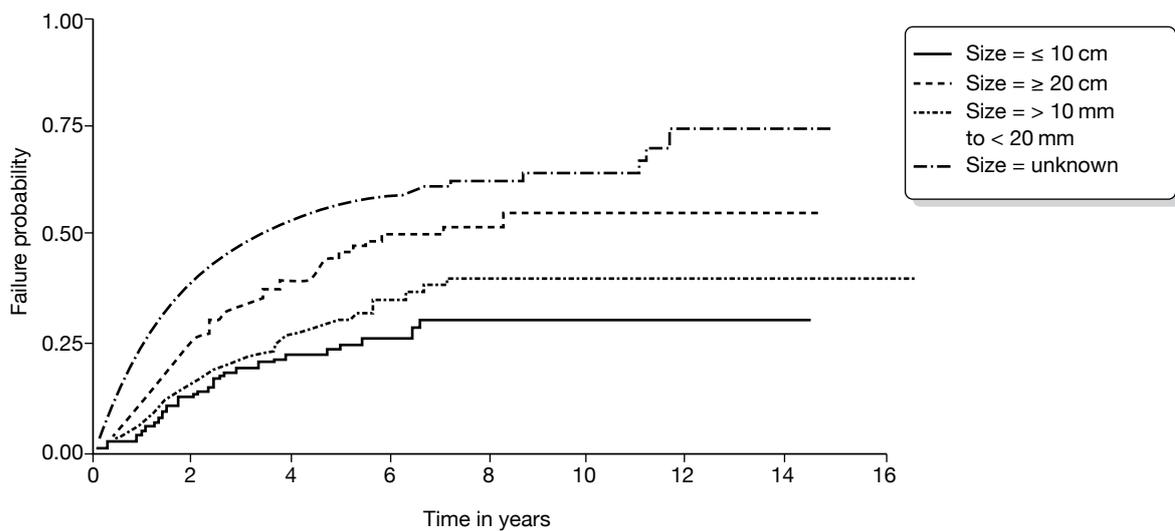
FIGURE 21 Kaplan–Meier failure curves for IBTR cohort for time to death from breast cancer by size of second tumour.

There were 975 women with 4268 years of follow-up in the MCBC tumour cohort, with 358 deaths from all causes and 23 deaths from breast cancer. Median time from diagnosis of primary tumour to diagnosis of second tumour was 52 months.

Estimates from Cox regression models for time to death from all causes in the MCBC cohort are shown in *Table 26*. Women with a second tumour of ≥ 20 mm in maximum diameter were at an elevated risk of death compared with the reference group of ≤ 10 mm, HR 2.14 (95% CI 1.49 to 3.06). This was also evident from the Kaplan–Meier failure curves shown in *Figure 22*.

Estimates from Cox proportional hazards regression models for time to death from breast cancer in the MCBC cohort are not included. This was because of the relatively few deaths recorded from breast cancer (see *Table 25* and *Figure 23*). A univariate analysis of the size of second tumour showed that women with a second tumour of ≥ 20 mm in maximum diameter were at an

TABLE 26 Cox proportional hazard regression models for time to outcome in the IBTR and MCBC occurrence cohorts

	Cox model for time to death from:								
	All causes in patients with IBTR			Breast cancer in patents with IBTR			All causes in patents with MCBC		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Size of second tumour (mm)									
≤10	(1.0)			(1.0)			(1.0)		
>10 to <20	1.04	0.75 to 1.43	0.821	1.24	0.84 to 1.83	0.269	1.28	0.89 to 1.85	0.187
≥20	1.75	1.29 to 2.37	<0.001	1.99	1.37 to 2.89	<0.001	2.14	1.49 to 3.06	<0.001
Size unknown	1.97	1.49 to 2.59	<0.001	2.15	1.53 to 3.03	<0.001	3.18	2.24 to 4.53	<0.001
Time to second tumour (months)									
<60	1.66	1.35 to 2.04	<0.001	2.08	1.60 to 2.70	<0.001	1.29	1.01 to 1.63	0.040
≥60	(1.0)			(1.0)			(1.0)		
Age (years)									
≤34	0.82	0.54 to 1.24	0.348	0.85	0.53 to 1.35	0.485	0.73	0.41 to 1.31	0.299
35–49	0.88	0.71 to 1.09	0.228	0.94	0.74 to 1.20	0.637	0.95	0.72 to 1.24	0.686
50–64	(1.0)			(1.0)			(1.0)		
65–74	1.31	1.04 to 1.64	0.022	1.17	0.89 to 1.53	0.269	1.58	1.17 to 2.12	0.003
75–79	1.42	1.04 to 1.93	0.028	1.22	0.83 to 1.79	0.303	2.78	1.79 to 4.31	<0.001
80+	1.51	1.08 to 2.11	0.016	1.03	0.66 to 1.62	0.894	2.28	1.20 to 4.31	0.011
Grade									
1	(1.0)			(1.0)			(1.0)		
2	1.58	1.10 to 2.26	0.013	2.24	1.35 to 3.72	0.002	1.32	0.90 to 1.93	0.151
3	2.10	1.46 to 3.00	<0.001	3.06	1.85 to 5.07	<0.001	1.25	0.84 to 1.86	0.269
Unknown	1.16	0.74 to 1.80	0.522	1.54	0.84 to 2.82	0.161	1.47	0.96 to 2.24	0.079

continued

TABLE 26 Cox proportional hazard regression models for time to outcome in the IBTR and MCBC occurrence cohorts (continued)

	Cox model for time to death from:								
	All causes in patients with IBTR			Breast cancer in patients with IBTR			All causes in patients with MCBC		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Size (mm)									
≤10	(1.0)			(1.0)			(1.0)		
>10 to <20	1.27	0.88 to 1.83	0.194	1.45	0.90 to 2.33	0.123	1.50	0.94 to 2.41	0.091
≥20	1.41	0.98 to 2.02	0.065	1.60	1.00 to 2.55	0.050	1.79	1.11 to 2.90	0.018
Size unknown	1.18	0.79 to 1.74	0.419	1.48	0.90 to 2.44	0.123	1.33	0.78 to 2.27	0.289
Nodes									
0	(1.0)			(1.0)			(1.0)		
1–3	1.32	1.04 to 1.67	0.021	1.39	1.06 to 1.82	0.016	1.52	1.12 to 2.07	0.007
4+	1.51	1.17 to 1.94	0.002	1.51	1.13 to 2.02	0.005	2.82	2.02 to 3.93	<0.001
Unknown	1.18	0.92 to 1.50	0.195	0.99	0.72 to 1.35	0.934	1.78	1.32 to 2.41	<0.001
Vascular invasion									
No	(1.0)			(1.0)			(1.0)		
Yes	1.35	1.10 to 1.67	0.005	1.48	1.16 to 1.89	0.002	1.71	1.28 to 2.28	<0.001
Unknown	1.37	1.08 to 1.74	0.009	1.39	1.04 to 1.86	0.027	1.52	1.14 to 2.02	0.005
Surgery									
Lumpectomy	(1.0)			(1.0)			(1.0)		
Mastectomy	1.40	1.17 to 1.68	<0.001	1.51	1.22 to 1.86	<0.001	1.19	0.93 to 1.52	0.164
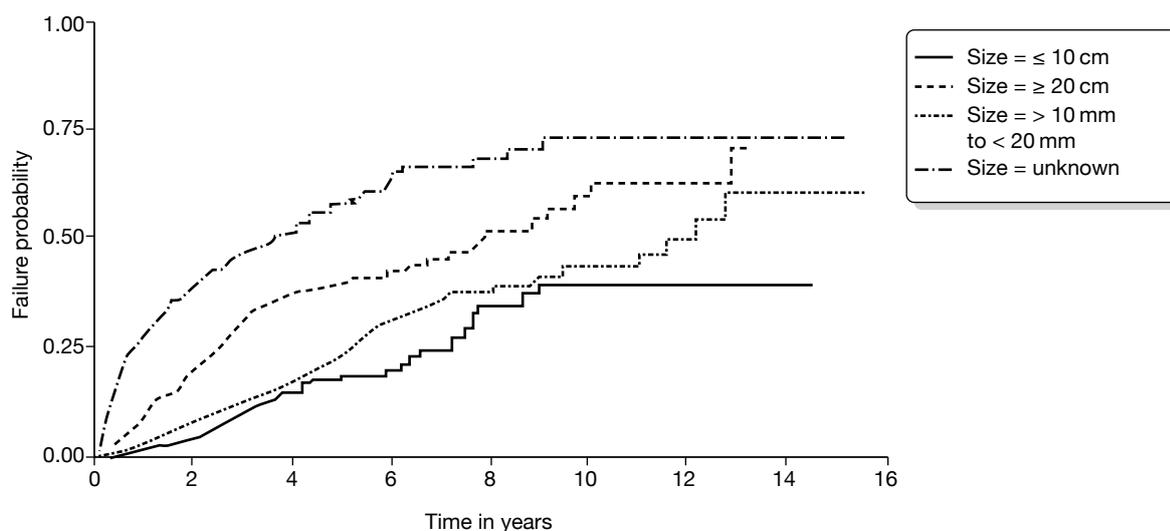
FIGURE 22 Kaplan–Meier failure curves for MCBC occurrence cohort for time to death from all causes by size of second tumour.
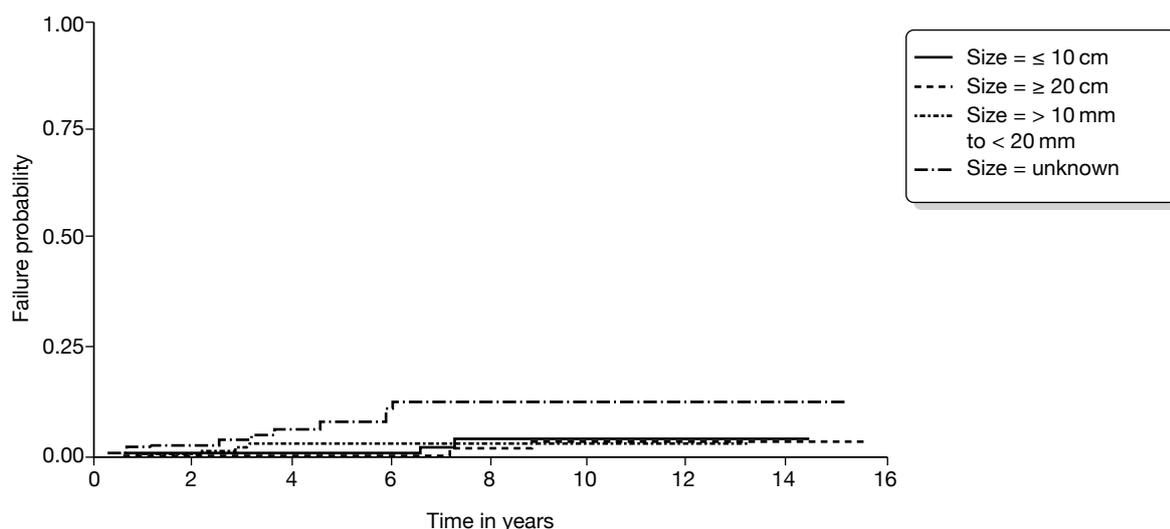
FIGURE 23 Kaplan–Meier failure curves for MCBC occurrence cohort for time to death from breast cancer by size of second tumour.

elevated risk of death compared with the reference group of ≤ 10 mm, HR 1.99 (95% CI 1.38 to 2.83) (see also *Figure 23*).

Edinburgh breast cancer data set

We also analysed a smaller but cleaner data set from Edinburgh to confirm risk factors for IBTR and MCBC, and also risk factors for all-cause death and breast cancer death. This analysis is included in *Appendix 26*. In summary, this analysis confirmed the findings from the WMCIU analysis. Women who experienced IBTR were at an increased risk of death from all causes (HR 1.87, 95% CI 1.41 to 2.49) and of death from breast cancer (HR 2.69, 95% CI 1.94 to 3.72). This was not true for women who experienced MCBC; there was no evidence that these women were at increased risk.

Summary

The WMCIU data set confirms the known risk factors for death from breast cancer, which are tumour size, grade, lymph node involvement, lymphovascular invasion and age, and demonstrates that IBTR is an independent variable affecting survival. This was also confirmed in a second data set. However, the occurrence of MCBC did not adversely affect survival. In those women experiencing a second tumour, the size of the second tumour is important, with tumours of > 20 mm in maximum diameter being at a significantly greater risk of death than those with either no second tumour or those with a second tumour < 10 mm in maximum diameter.

We have shown that IBTR has an adverse effect on survival. This is independent of the primary tumour and in our analysis of BCS the HR was 2.13 (95% CI 1.78 to 2.56). This has been found in several previously published series.[20,77–80] Furthermore, the time to the event is important, with those events that happen later having a survival advantage compared with those that occur earlier. This was also found in a combined analysis of five National Surgical Adjuvant Breast and Bowel Project trials of women treated by BCS who had node-negative disease[77] and the Tuscan second breast cancer case series.[81]

Chapter 7

Economic evaluation

Introduction

This chapter has four main sections: a brief outline of the principles of economic evaluation, followed by sections reporting the methods, results and summary of the findings of the economic evaluation.

The objectives of this chapter are to determine whether or not (1) any method of surveillance could potentially be cost-effective for the whole population of women eligible for the service and (2) the method of surveillance should be varied between subgroups of women who are eligible for surveillance following surgery for breast cancer.

Principles of economic evaluation

A brief introduction to economic evaluation

The decision to use resources to provide one method of breast cancer surveillance means that the opportunity to use these resources in other desirable ways (either to provide another method of surveillance or to meet an entirely different health need) is given up. The cost of this decision is the benefits (health gains, etc.) that could have been obtained had the resources been used in another desirable way. This is the economic notion of 'opportunity cost'. Strictly speaking, the opportunity cost of a decision to use resources in one way is equivalent to the benefits that could have been obtained had the resources been used to provide the next best alternative. Economic evaluation is a method of providing decision-makers with information about the opportunity cost of the decisions that could be made. It does this by comparing alternative courses of action in terms of both their costs and consequences.[82]

An economic evaluation in this context would involve assessing the relative costs and benefits associated with alternative surveillance regimens for breast cancer. The objective of such an economic evaluation would be to provide information to assist decision-makers in the allocation of available resources so that benefits could be maximised. A cost-effectiveness plane (*Figure 24*) illustrates how an economic evaluation brings together information on costs and benefits. The vertical axis represents the difference in costs between surveillance regimens (e.g. mammography vs MRI). The horizontal axis represents differences in effectiveness between the two regimens.

In the north-west and south-east quadrants of *Figure 24* a clear decision about which surveillance regimen should be preferred is provided because one or other regimen is less costly but more effective (i.e. it dominates the other treatment). In the north-west quadrant the experimental regimen is more costly and provides less benefit, therefore the control regimen is more efficient (is dominant). In the south-east quadrant the opposite situation occurs and the experimental regimen is more efficient (is dominant), as it is less costly and provides more benefit. The circle in the centre of the figure represents the possibility that no meaningful differences in costs or benefits exist between the regimens and for practical purposes the two regimens are equally efficient.
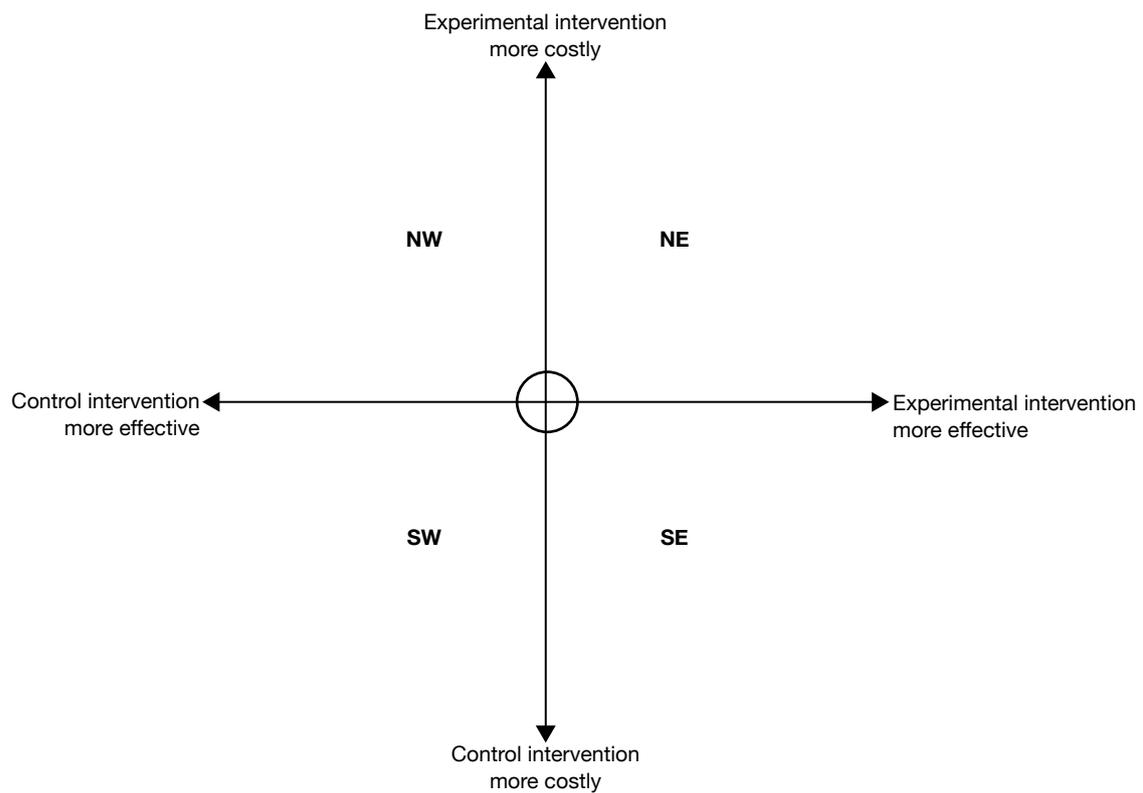
FIGURE 24 Relationship between the difference in costs and effects between a new (experimental) method of surveillance and an alternative (control) method. NE, north-east; NW, north-west; SE, south-east; SW, south-west.

In the two remaining areas of the figure, the north-east and south-west quadrants, a judgement is required as to whether the more effective regimen is worth the extra cost. To aid these judgements, information can be provided in terms of an incremental cost-effectiveness ratio (ICER). The higher the ICER of one intervention compared with another, the less likely it is that this intervention will be considered efficient.

Methods

Economic modelling of alternative surveillance regimens

A surveillance programme needs to be not only effective, but also cost-effective. Using Markov modelling methods, the cost-effectiveness of various surveillance programmes is compared. The economic model describes the pathway of care of individuals from the point where they received treatment for breast cancer and will receive some form of ongoing surveillance. This includes their longer-term (ideally their lifetime) costs and consequences, including those that might arise from any subsequent cancers. Surveillance can be considered as an event undertaken at discrete intervals and repeated over time and hence a Markov model was developed. This can be used to describe the logical and temporal sequence of events following the implementation of alternative surveillance regimens. We used the model to provide the estimated costs and outcomes for a selected period for a cohort of women for different surveillance regimens.

The model

Markov models comprise a set of states and at any point in time an individual will be in one of these states and will stay in that state for a defined period of time (the cycle length) before they

are allowed to move to another state. The cycle length must be a period relevant to the condition considered (e.g. 6 months, 1 year, 18 months, etc.) At the end of each cycle, individuals can remain in the state in which they started the cycle or move to a different state. The probabilities of moving from one state to another are called *transition probabilities*. In each state, the model will assign costs and benefits for each individual according to different interventions and/or time spent in each state. In a Markov model, there must be at least one absorbing state, typically death, from which the person will not be able to leave.

Figure 25 shows a simplified version of the model presented for illustrative purposes (*Appendix 27* contains a copy of a section of the full model structure). In this figure, the states are presented as ovals, whereas the arrows show the possible directions in which individuals could move at the end of each cycle. The rate at which an individual moves (makes a transition) between states is governed by the transition probabilities. The states considered in the model are thought to reflect possible paths of individuals. The top line in *Figure 25* represents the possible path for individuals who start off after 'successful' (the belief being that the woman has been successfully treated for cancer but is at risk of developing subsequent disease) treatment free from cancer but who develop breast cancer over time but remain undiagnosed. The bottom section of *Figure 25* represents those individuals who start in the model after 'successful' treatment free of cancer, but go on to develop IBTR or MCBC over time but are identified and treated for the disease.

If a woman initially has no evidence of IBTR or MCBC then over time she will have the chance of IBTR or MCBC occurring. The natural history of disease and the effectiveness of initial treatment determine the chance of this occurrence. Surveillance will not alter the chance of IBTR or MCBC occurring but may alter the chance of that cancer being detected, the stage at which it is found and hence the treatment and possible final outcome. Within the simplified version of the model shown in *Figure 25* only three treatment states are depicted. These treatment states vary according to the risk profile of the breast cancer being treated. Once IBTR or MCBC is identified it is assumed that the cancer is treated and that subsequently individuals may have an altered life expectancy as a result of the recurrence. We also assumed that women who have had a further cancer will be judged as being at 'moderate' risk of developing further disease and so will have a more intensive follow-up. The absorbing state in the model is death. Any individual can move into this state from any other state within the model. The chance of moving into this state will be determined by the age of the woman through all-cause mortality and cancer-specific mortality. If a cancer is missed during surveillance then it is assumed that it will remain untreated until it is identified.
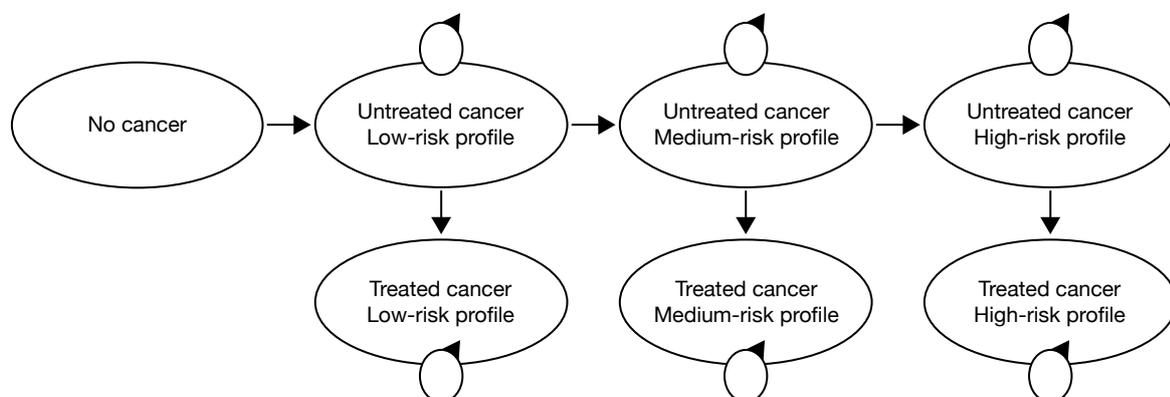
FIGURE 25 Depiction of a simplified version of the Markov model. Risk profile refers to the mortality risk for a given cancer. In this simplified figure, it is assumed that cancers differ in terms of the risk of death.

The model will compare different regimens but, for each regimen, a cohort of women will pass through the different health states. The costs per woman and speed at which they progress through the states will vary between regimens. The intuitive idea behind the model is to identify the regimen that leads to the most effective and cost-effective surveillance regimen.

Description of a woman's movement through a model regimen

The model includes women who may develop IBTR and or MCBC. The model itself does not differentiate between these situations. The model starts with a surveillance year; based on information from the survey of current practice this frequency could be once every 6, 12, 18, 24 or 36 months. In regimen 1, individuals can either be followed up using surveillance mammography or present to their GP with a symptom, i.e. discover a lump. Women who have a mammogram can either be identified as free of disease or have a positive mammogram. The model structure allows this to be either a true- or false-positive or a true- or false-negative. If the mammogram is a true-negative, individuals will then go back to the surveillance programme. If the mammogram is a false-negative, individuals also return to the surveillance programme, but these individuals would not receive any treatment or care for that cancer although it remains undetected. Furthermore, it is possible that if a cancer is undiagnosed or untreated the severity of the cancer will increase and the prognosis worsen, for example over time the tumour may increase in size. We handle this within the model by increasing the severity of untreated disease over time. It is also possible for individuals who have had a true-negative, over the duration of the cycle, to go on to develop breast cancer in a subsequent cycle. The likelihood of this happening will be dictated by the expected incidence of IBTR and MCBC over the cycle length (for example, if the cycle length were 1 year then it would be based upon an estimate of the annual incidence of IBTR and MCBC).

If the mammogram is a true-positive, individuals will be diagnosed with invasive or non-invasive cancer and managed appropriately. If the mammogram is a false-positive it will be assumed that the individual will undergo further invasive tests and on a negative finding of these tests they will return to the surveillance programme at the end of the cycle.

The regimens considered

We outlined the alternative surveillance regimens in *Chapter 3* (see *Methods for the survey*). The intention was to compare each of these within the economic model. We planned to combine surveillance regimens for hypothetical cohorts of the population defined in terms of the nature of primary disease, treatment and demographic characteristics, etc. These cohorts reflect the prior hypothesised risk of IBTR and MCBC in the population of women previously treated surgically for a primary breast cancer.

As described in *Methods for the survey*, we identified nine different surveillance regimens. We reduced these to three regimens, which we felt broadly represented the most relevant comparators. Furthermore, as reported in *Chapter 5*, few data on the diagnostic performance of the alternative methods of identifying a breast cancer were available. Consequently, it was not possible to model all of these options. However, some data were available to facilitate the modelling of mammographic surveillance with and without clinical follow-up organised either through secondary care or through the screening service. The presentation of the woman following referral from primary care following the identification of a suspicious lump on self-examination was also modelled. We used this form of diagnosis in two specific ways within the model. First, we used it to define a situation where no formal surveillance is used. It is also used to model the possibility that a woman presents between surveillance points with symptoms suggestive to a GP of breast cancer, for example if surveillance is performed every 36 months then within this 36-month interval the model will allow a woman to present with clinical symptoms that are suggestive of breast cancer and for this cancer to be identified.

Populating the model with parameter estimates

To provide estimates of relative cost-effectiveness, the model requires estimated values for a range of different types of parameters. Such parameter estimates should be derived in a systematic and reproducible manner to avoid bias caused by the distorted and selective use of data.[50] The assembly of such data need not necessarily be comprehensive; rather, effort should focus on identifying the most relevant data to the decision problem, which in this case was the comparison of alternative surveillance regimens for women after treatment for primary breast cancer.

We assembled the different types of data required for the economic model from analyses of existing data sets, a series of systematic reviews, and focused searches for specific pieces of data. We report the methods and results of the reviews and analyses of existing data sets in detail in *Chapters 4–6*. In brief, the broad types of data required to populate the economic model relate to:

- the uptake of surveillance and follow-up
- the prevalence, incidence and risk of progression of the disease, i.e. its epidemiology and natural history
- the performance of different regimens (e.g. clinical examinations, mammograms, etc.) in terms of the accuracy of the diagnostic tests
- resource use and unit costs required to estimate the costs of alternative surveillance regimens; the specific parameters and methods used to provide estimates that are relevant to the UK context
- health-state utilities.

Within the model, we based estimates of uptake upon simplifying assumptions and advice from the members of the project Advisory Group. We derived the data on the natural history of women from the analysis of the large data set reported in *Chapter 6*. Further data relating to the management and outcomes came from the source data used to inform recent NICE guidelines.[24]

We derived information on the diagnostic performance of different types of clinical tests, for example the accuracy of mammography, from data reported in *Chapter 5*.

We derived data on the costs incurred for the different surveillance regimens and their consequences from structured reviews of the published literature, as well as routine data sources such as the *NHS Reference Costs*.[40] The perspective for costs is the NHS.

Data on the utilities associated with differing severities of cancer and the possible differences in quality of life associated with various surveillance regimens were obtained from the published literature, including the review of economic evaluations, as described above, as well as a search of the Cost-Effectiveness Analysis Registry (CEA Registry: www.cearegistry.org/).

We report how we derived each of these sets of data and the values used in the model in more detail in the sections below.

Uptake of surveillance and follow-up

Within the model, we assumed that, if individuals are invited to attend surveillance, they do in fact attend. This may be too high, as approximately 75–80% of the normal population attend for breast screening. The other variable required for the model is the probability that a woman will present to the GP with symptoms that she thinks are suspicious. Based upon advice from the clinical members of the Advisory Group we assumed that 30% of women with prior treatment for breast cancer might present to the GP per annum. We then converted this percentage into a probability of presenting per 6-month cycle by fitting an exponential curve. The probability used within the model was 0.1393, i.e. in the no surveillance arm of the model, and for during the

surveillance interval in the surveillance arms of the model, just under 14% of surviving women who have not been diagnosed with a recurrent cancer will present to a GP every 6 months. The following formula assumes that events occur at a constant rate over time: $p = 1 - e^{-rt}$, where p = probability, e = base of natural logarithm, r = rate and t = time period.

Epidemiology and natural history of breast cancer

Data relating to the natural history of breast cancer required for the model can be split into four components. These are:

1. recurrence/occurrence rates for women initially treated for breast cancer
2. estimated survival of women without and with IBTR or MCBC
3. estimated proportions of the different types of IBTR or MCBC occurring
4. estimated change in the severity of untreated cancer over time.

IBTR and/or MCBC rates for women initially treated for breast cancer

Part of the analysis reported in *Chapter 6* related to the time to event for IBTR and MCBC cancers. Using the estimated 10-year survival and the same methods as described above, an exponential curve was fitted so that the probability of experiencing an event for IBTR or MCBC per cycle (a 6-month period) was estimated. We report the estimated 10-year incidence rate for women initially treated by BCS or mastectomy, as well as the incidence per cycle (per 6-month period) in *Table 27*. Within the model, we assumed IBTR and MCBC events were independent and that the rates summed within the model to provide a net rate of cancer incidence. As described below this assumption was relaxed in sensitivity analyses, where we modelled the impact on costs and benefits of the incidence of the more serious IBTR events separately.

The data reported in *Table 27* are taken to be representative of the rates expected for the whole population of women who received either BCS or mastectomy as part of the treatment of their primary cancer. It should be noted that the rates of MCBC in women who were originally treated by mastectomy are higher than the rates in those who were originally treated using BCS. These estimates are based upon observed estimates and the difference may simply be a reflection of imprecision in estimates, i.e. in reality no difference exists. Whether this is true or not is a matter for debate. A finding from *Chapter 6* was that the incidence of subsequent cancer events was predicted in part by the characteristics of the primary cancer. Using the same methods described we have estimated the incidence per cycle for the reference case used in Cox proportional hazard models reported in *Chapter 6* (*Table 28*).

We calculated upper and lower estimates of incidence by combining estimates of the hazard rates obtained from the Cox proportional hazard models with the event rates and probabilities reported in *Table 29*. It was assumed that hazard rates were additive but upper and lower estimates were based only on proportional hazard rates for factors, for example tumour size, age, grade, etc., which were found to be statistically significant at the 5% level in the analyses reported in *Chapter 6*.

TABLE 27 Estimated incidence of IBTR and MCBC disease for women following surgery for primary disease

Initial form of surgery	Type of event	10-year failure probability	6-month cycle failure probability
BCS	IBTR	0.045	0.0023
	MCBC	0.030	0.0015
Mastectomy	IBTR	0.035	0.0018
	MCBC	0.035	0.0018

TABLE 28 Alternative values for the subgroup of women taken as the reference case in Cox proportional hazard model[a]

Initial form of surgery	Type of event	10-year failure probability	6-month cycle failure probability
BCS	IBTR	0.040	0.0020
	MCBC	0.020	0.0010
Mastectomy	IBTR	0.038	0.0019
	MCBC	0.028	0.0014

a The reference group in the Cox proportional hazard model was: age 50–64 years, grade 1, size < 1 cm, no lymph node involvement, no vascular invasion.

TABLE 29 Hazard rates for high and low estimates and the incidence per cycle estimated from these rates

Initial form of surgery	Type of event	Cumulative hazard rate		6-month cycle failure probability	
		Low	High	Low	High
BCS	IBTR	0.72	6.64	0.0015	0.0135
	MCBC	0.34	1.60	0.0003	0.0016
Mastectomy	IBTR	0.85[a]	5.36	0.0016	0.0104
	MCBC	0.27	1.53	< 0.0014	0.0022

a There was no evidence of a statistically significant difference. The smallest point estimate of a difference was for age 35–49 years.

Estimated survival of women with and without IBTR and/or MCBC

The economic model does not stop with the diagnosis of cancer. It seeks to model the impact on survival caused by delayed identification. To do this estimates of survival of women who develop a further case of cancer are required. Also required are estimates of survival for those women who do not develop further cancer. Estimates of the former depend upon whether or not the cancer was diagnosed and treated and the effectiveness of any treatment.

We conducted a structured review of relevant management guidelines to estimate data on the survival of women who go on to develop further cancer (reported in more detail in *Appendix 28*). The recent NICE guideline was identified as providing the best available evidence of treatments for early breast cancer relevant to the UK.[24] The data used to support the NICE guideline recommendations came from the EBCTCG[83] and Adjuvant! Online computer program.[84] We prepared estimates of survival following various treatment options using the Adjuvant! Online computer program due to its flexibility. Adjuvant! Online draws on information from mortality statistics in the USA, the SEER database, and meta-analyses and individual clinical trials. Based on well-validated factors, such as age, menopausal status, oestrogen receptor (ER) status, tumour size and grade, nodes status, etc., predictions can be made about survival for alternative adjuvant treatment regimens, such as chemotherapy and hormone therapy. The programme derives survival estimates from the US population, however.

As survival estimates are linked to the effectiveness of treatments it was necessary to also define the therapy given for a cancer. The choice about what therapies would be adopted for which categories of cancer were based upon the recommendations in the NICE guideline[24] and clinical advice from members of the study team about typical treatments within the UK. Based upon these data we derived specific therapies for cancers with specific characteristics. Using Adjuvant! Online, we estimated predictions of 10-year cancer-related mortality. *Table 30* shows the simplified classification of prognostic factors used by Adjuvant! Online. We grouped these

TABLE 30 The simplified classification of prognostic factors

Comorbidity	Average for age			
ER status	Positive		Negative	
Tumour size (cm)	0.1–2		2.1–5	>5
Positive nodes	0	1–3	4–9	>9
Tumour grade[a]	1		2	3

a   Excluded factors in current subgroups.

estimates, as described below, for cancers that had similar management costs and survival. This simplification was performed because Adjuvant! Online can provide more data than were readily manageable in the economic model, and the economic model itself was focused on surveillance regimens rather than treatments of women with breast cancer.

We grouped the different cancers into five different risk profiles, which had an increasingly worse prognosis. The cancers included in each risk profile had a predicted 10-year mortality that fell into the range defined for the risk profile. We derived the range for each risk profile following consideration of the mortality data derived from Adjuvant! Online and discussions within the Advisory Group.

As each risk profile contained several different cancers (defined in terms of size, ER status, etc.) an average mortality had to be calculated. To calculate this average mortality we required data on the estimated proportion of each type of cancer in each risk profile. These data were derived from the further analysis of the WMCIU Breast Cancer Registry data set used in *Chapter 6*. Cases were included if they were invasive tumours and diagnosed from 1997 (due to the extent of missing data prior to that date). We considered only tumours that were surgically treated. For the selected cases, descriptive information about the proportions of women with cancers with the following combination of characteristics were derived: ER positive or negative, grade of cancer (grades 1, 2 or 3), tumour size (0.1–2.0 cm, 2.1–5.0 cm, > 5.0 cm) and number of positive lymph nodes (zero, one to three, four or more). Unfortunately, ER status was mostly missing within the data set so could not be provided. Therefore, using published information[85] we considered that 70% of cancers would be ER positive with the remainder being ER negative. We report these data in detail in *Appendix 28*. We assumed that the proportions of the different types of IBTR and MCBC would be the same as those for primary cancer. We made this assumption because there were more cases of primary cancer and hence less likelihood of there being no data to provide estimates for the combination of tumour characteristics described below.

From the WMCIU Breast Cancer Registry data, the proportion of each type of cancer (in terms of the proportion with a particular tumour grade, size, nodal involvement, etc.) was defined in each risk profile. We then multiplied the proportions by the 10-year mortality estimates for the corresponding cancer. We then summed the product of these calculations to give an average 10-year mortality rate for each risk profile.

Using the estimated 10-year mortality derived for each risk profile we fitted an exponential curve so that the probability of dying from cancer per cycle (a 6-month period) for each risk profile (*Table 31*) could be estimated using a formula similar to the one described above. For example, *Table 31* shows that the average mortality rate from cancer at 10 years for risk profile state 1 was 4.86%, and, using the formula reported above, the risk of dying from cancer in any 6-month cycle was estimated to be 0.002%. Further detail of the data underpinning *Table 31* is shown in *Appendix 30*.

TABLE 31 Mortality rates (%) from breast cancer at 10 years and per 6-month cycle for each risk profile (data used within the model)

Risk profile	10-year mortality rate	6-month cycle mortality rate
1	4.86	0.002425
2	12.47	0.006217
3	21.19	0.010539
4	36.81	0.018236
5	57.20	0.028197

This formula used to estimate the probability of dying from cancer per cycle (a 6-month period) assumes that deaths occur at a constant rate over time. If mortality is positively skewed then for a shorter time horizon of the model this may represent an underestimate of mortality, and it may overestimate mortality for longer time horizons. The cancer mortality data also assume that risk of death from cancer is independent of the women's age; this may underestimate the risks from cancer in younger women (i.e. those under 50 years of age).

These mortality rates are based on data for women who have received treatment for breast cancer. Therefore, they may not be applicable to women whose cancer is untreated because it is undetected. We hypothesised that at each time point a woman with an untreated cancer would face a higher risk of death in the next cycle (6-month period) than an identical woman whose cancer had been treated. This increased risk of death was proxied by comparing the estimated risk of dying at 5 years following a diagnosis of cancer for a woman diagnosed with cancer in the period 1980–4 with the risk for an identical woman from 2000 to 2004. The data used to derive the parameter value used in the model came from information produced by the Information and Statistics Division of NHS Scotland.[86] The base-case value was based upon all women aged 15–74 years. In this group of women, expected 5-year mortality for women diagnosed between 1980 and 1984 was 34.9%. In the period 2000–4 the expected 5-year mortality was 14.9%. The ratio of these two numbers gives a value of 2.34. This value was used to inflate the 6-month breast cancer mortality rates reported in *Table 31*. *Table 32* summarises the base-case and high and low values used within the model. Low and high values are based upon the lowest and highest values obtained for any age grouping reported by the Information and Statistics Division of NHS Scotland.

Within the base-case analysis we assumed that an IBTR that fits within a given risk profile will have the same probability of death per 6-month cycle period as an otherwise identical MCBC. The data reported in *Chapter 6* suggests that mortality following IBTR may be substantially higher than the mortality for an otherwise identical MCBC, however. As noted above, we conducted sensitivity analyses to explore the impact of the increased risk of death from IBTR. We derived the increased risk of death per 6-month period by multiplying the HR for mortality from IBTR reported in *Chapter 6* with the mortality rates for treated and untreated cancers. The point estimate for the hazard rate for death for IBTR was 1.76 (with an upper value from the 95% CI of 2.13). We used the extremes of the CIs for this hazard rate to define low and high rates within the model.

Data were also required on all-cause mortality. These data were required because women who do not develop cancer still have a chance of dying from other causes. In addition, women who do develop cancer also have the risk of dying from other causes. For both sets of women as they age within the model, mortality will increase. Estimates of all-cause mortality were obtained from the published UK life tables for the years.[87] From these data a mortality rate for each 6-monthly cycle was calculated using the previously defined formula. This is reported in detail in *Appendix 31*.

TABLE 32 Summary of breast cancer mortality inflators used within the model to derive breast cancer mortality for those with undiagnosed breast cancer

| | 5-year mortality | | | |
	Cancer detected 1980–4 (%)	Cancer detected 2000–4 (%)	Inflator	Notes
Base case	34.9	14.9	2.340	Based on the cohorts of women aged 15–74 years at time of diagnosis
Low estimate	36.4	12.5	1.508	Based on the cohorts of women aged 75–84 years at time of diagnosis
High estimate	39.1	25.9	2.916	Based on the cohorts of women aged 55–64 years at time of diagnosis

Estimated proportions of the different types of IBTR and/or MCBC cancers occurring

For the model, information was needed not just on whether a cancer occurs or not, but also on the severity of that cancer. We assumed that at the point where a cancer technically becomes detectable the size of the cancer is below 1 cm in diameter. In terms of the risk profile classification defined above we further assumed that all these people are initially in risk profile category 1 at the point when the cancer becomes detectable. Over time, an undetected cancer will increase in severity and the estimates used to model this are described below.

Estimated change in the risk profile of untreated cancer over time

One variable required for the economic evaluation is the rate at which an undiagnosed cancer may move to a worse risk profile (with a consequent reduction in life expectancy and quality of life and an increase in treatment costs). We sought data on which to base estimates for this variable from a structured review of the literature relating to doubling time of a breast cancer and the factors, for example grade of cancer, which might affect the doubling time of tumours. We sought these data as the individual patient analysis reported in *Chapter 6* found that a significant predictor of mortality was tumour size, with larger-sized tumours having a shorter life expectancy than smaller tumours.

It is recognised that there is a considerable degree of uncertainty about the rates of growth of breast cancers.[88] However, data were sought about plausible rates of growth and about potential range in the rates of growth that can be explored in a subsequent sensitivity analysis. A summary of the findings of this structured review is reported in *Appendix 32*. Given the information found in this review of the literature, it is clear that there is little consensus on the doubling times of breast cancer tumours. The data we have used in the economic model are based on the information provided by Peer and colleagues,[89] taking the mean doubling time in tumour volume to be 157 days. We tested the consequences of this in a high/low sensitivity analysis where we will vary this rate between the plausible extremes of the data presented in *Table 33*.

To use information on the mean doubling time within the model we had to estimate how long it would take a tumour of the minimum technically identifiable size to increase in size, where an untreated tumour would move from one risk profile to a risk profile with a worse prognosis. We took the minimum diameter of a detectable cancer to be 0.75 cm. This value was taken because the volume of a cancer with this diameter is close to the minimum volume size considered by Adjuvant! Online. The data on time to reach the threshold tumour size were converted into risks of increasing the risk profile by one level for each cycle that a cancer remains untreated. We performed this using the same methods described above to estimate incidence and mortality rates.

Diagnostic performance of tests

As reported in *Chapter 5*, relatively few data were available on the diagnostic performance of any of the tests. Within the model, we assumed that at the time a woman receives a diagnostic test as part of surveillance she is asymptomatic.

For IBTR, we based data on data reported in *Chapter 5*, and summarised in *Table 20* (*Chapter 5*), and on discussions with the clinical experts involved in the study. Where relevant published data were available in the absence of pooled data the study judged to be closest to the median of reported results was used to inform the values chosen for the base-case analysis. We used data from other studies to define plausible extremes. Where it was feasible for these tests to be used then they were also used for MCBC, as few additional data were available (*Table 34*).

For surveillance mammography the values used in the base-case analysis were based upon those derived from Drew and colleagues.[67] We based low and high estimates of sensitivity upon the ranges for these parameters reported in *Table 20* (*Chapter 5*). These data represent extreme values that will be used in the sensitivity analysis.

As reported in *Chapter 5*, only one study provided data on the sensitivity and specificity of mammography and clinical follow-up. These data did not seem plausible (e.g. the reported sensitivity was 100%). The values reported in *Table 34* are assumptions derived following discussions with clinical experts. The consensus of opinion was that the combination of follow-up and mammography would slightly improve the sensitivity and specificity. In a sensitivity analysis we will explore the impact of changing these values between high and low estimates. We will also seek to identify whether there is a threshold in terms of diagnostic performance, which would make the additional cost of clinical follow-up worthwhile.

TABLE 33 Mean breast cancer doubling times by age

Age at diagnosis (years)	Mean doubling time (days)	Time for a 0.75-cm diameter tumour to move up one risk profile (days)	6-month rate for increase in risk profile
< 50	80	300	0.2623
50–70	157	540	0.1555[a]

a　Value taken in the base-case analysis.
Source: Peer and colleagues.[89]

TABLE 34 Diagnostic performance of the different tests

Test	Parameter	Base-case value (%)	Low (%)	High (%)
Surveillance mammography	Sensitivity	67	65	70
	Specificity	85	65	90
Surveillance mammography and clinical follow-up	Sensitivity	75	70	80
	Specificity	90	70	95
Clinical examination	Sensitivity	35	25	50
	Specificity	35	25	50
Rates available for other tests explored in a sensitivity analysis				
MRI	Sensitivity	67	65	70
	Specificity	85	65	90

Within the model, data are also required for the diagnostic performance of a clinical examination when performed by a GP. Again, few data were available and following discussions we assumed that the rates used within the model would be slightly lower than those reported in the systematic review of diagnostic performance (*Chapter 5*).

We considered the impact of using a higher cost but more effective diagnostic test. As a proxy for such a test data were based upon the performance of MRI. It should be noted that the values identified, especially at the upper level, are where MRI has been used in a higher risk group of women. Hence, the values are not necessarily illustrative of MRI itself but rather of a hypothetical test. The values for the base-case analysis were based upon those reported by Drew and colleagues[67] but it was assumed that the sensitivity was slightly less than perfect (i.e. 95% vs the 100% reported by Drew and colleagues).[65] Low values of sensitivity were based upon data from Warner and colleagues[90] who conducted a systematic review of prospective studies in which women at very high risk for breast cancer were screened with both MRI and mammography.[90] Hence even these data may not be fully representative of women eligible for surveillance mammography. The specificity values were informed by the estimates of one study[91] included in the Warner and colleagues review.[90] This study had the lowest specificity of any of the studies included in Warner and colleagues' 2008 study.[90]

Costing data

The costs of surveillance were broken down into the following cost categories:

■ Cost of:
  – inviting women for screening
  – the surveillance test (e.g. mammogram, MRI, clinical examination)
  – health-care professional time (e.g. GP consultation, clinical examination)
  – further invasive tests (e.g. core biopsy)
  – treatment (e.g. mastectomy, radiotherapy, drug treatment).

Tables 35–37 show the cost estimates used in the economic model. All costs are reported in 2008 pounds sterling. *Table 35* shows the current cost of the alternative screening strategies. The cost of inviting women to attend screening was obtained from a recent HTA report.[92] The cost of the alternative surveillance tests were all derived from routine sources. The cost of a mammogram was based on information from the NHSBSP 2009.[93] The NHSBSP estimates the cost of a mammogram in England to be £37.50 per woman invited and £45.50 per woman screened. An alternative costing source was obtained from the Scottish Breast Screening Programme, which estimates the cost of a mammogram to be £77.80.[94] The implications of the variation in costs between Scotland and England were explored in a sensitivity analysis. The cost of an MRI was estimated as being twice the cost of that reported in the *NHS Reference Costs*[40] for an outpatient MRI. This is because an MRI on a breast takes twice as long as a normal MRI and involves the use of a contrast. The lower quartile and upper quartile of the *NHS Reference Costs*[40] for this category are used to inform sensitivity analysis. We derived the costs of a clinical examination from routine data sources. The cost of a GP clinical examination was obtained from the Personal Social Services Research Unit (PSSRU)[95] and was based on the average cost of a GP consultation. In addition, we also included the cost of a clinical examination conducted in a secondary care setting by either a consultant or non-consultant. These costs were obtained from *NHS Reference Costs*.[40] Information on the range of costs (lower and upper quartile) was also available and these were used as upper and lower estimates in sensitivity analysis.

The costs of further invasive tests were obtained from a NICE evidence review group (ERG) report[96] and inflated to current prices using the PSSRU inflation index. The cost of a mastectomy

TABLE 35 Cost of screening regimens

Type of test	Cost (lower quartile/upper quartile), [alternative] (£)	Source
Clinical examination – GP	36	PSSRU[95]
Clinical examination – consultant	86 (63 to 100)	*NHS Reference Costs*[40] (ref. 103)
Clinical examination – non-consultant	65 (55 to 75)	*NHS Reference Costs*[40] (ref. 103)
Mammogram	45.50 [77.8]	NHSBS[93] (Scottish Breast Screening Programme)[94]
MRI – outpatient	232 (165 to 269)	*NHS Reference Costs*[40] (ref. TDIAGIM_APC; RA03Z)

TABLE 36 Cost of invasive tests and treatments[98]

Type of treatment	Cost (low/high) (£)	Source
Core biopsy	126.6	ERG report[96]
Mastectomy	3429	ERG report[96]
Radiotherapy	2395.58 (1649.20 to 2784.80)	*NHS Reference Costs*[40] (based on 20 sessions)
Hormone therapy (per year): tamoxifen	29.92[a]	TA112[98]
Hormone therapy (per year): aromatase inhibitor	919.6 to 1115.4	TA112[98]
Chemotherapy (per six treatment) administrations	4137[a] to 9850	TA109[99]

a   Value taken in breast cancer analysis.

TABLE 37 Surveillance regimen: clinical examination plus mammography for women receiving hormone therapy

Surveillance regimen	Cost (£)
Screening invitation	10.45
Mammography + clinical examination (consultant)	45.50 + 86
On positive finding	
Core biopsy	126.6
Mastectomy	3429
Radiotherapy	2395.58 (20 sessions[a])
Drug treatment (tamoxifen)	29.92 (per year)

a   Based on information from the PRIME trial.[97]

was based on the same source, and inflated to 2008 prices. The cost of radiotherapy was based on the cost of complex treatment on a mega-voltage machine,[40] assuming that women get on average 20 sessions of radiotherapy. This assumption was based on information from the PRIME trial, which reported that, on average, women receive 20 sessions of radiotherapy.[97] Again, lower quartile and upper quartile estimates of the cost of a single session of radiotherapy will be used in a sensitivity analysis.

The costs of drug treatment, for example the cost of hormone treatment, chemotherapy and combined treatment, were obtained from recent NICE guidance. The cost of hormone treatment was based on information reported in the costing template for technology appraisal

guidance 112.[98] This included the costs of tamoxifen for 5 years and the cost of aromatase inhibitors (anastrozole or letrozole) for 5 years. The cost of chemotherapy was based on the costs reported in NICE technology appraisal guidance 109.[99] The cost of chemotherapy is based on the cost of two different regimens (TAC – taxotere, adriamycin and cyclophosphamide; FEC – fluorouracil, epirubicin and cyclophosphamide). This is based on six cycles of treatment.

Each risk profile consists of a series of different types of cancers (defined in terms of ER status, grade, size and number of lymph nodes involved). As described above, an average mortality for each risk profile was estimated by combining information on the expected mortality for each specific cancer within a risk profile with information on the proportion of women in that risk profile that had that specific type of cancer. Adjuvant! Online reports mortality by the type of adjuvant therapy used. The clinical members of the research team determined, based on UK practice, which specific cancer in a profile would receive hormone therapy and/or chemotherapy. Using information on the proportion of cancers in a given risk profile that would be treated with a given adjuvant therapy a proportion of a cost of a course of hormone treatment or radiotherapy was incorporated into the cost assigned to each risk profile.

Table 37 shows the costs of one surveillance regimen for a woman invited to screening and who received a clinical examination and a mammogram. The costs include the costs of screening, the mammogram and clinical examination, conducted by a consultant. On a positive mammogram, the woman would then go on to have further invasive tests to confirm the result (core biopsy). On a true-positive finding, the woman would have a mastectomy followed by radiotherapy, followed by drug treatment (depending on the severity of the IBTR or MCBC). We based the costs of treatment on a number of assumptions:

- It is assumed that all ER+ women will receive hormone treatment. It is assumed that those women who have an excellent prognosis (survival rate at 10 years of 96% or greater) and are postmenopausal will receive tamoxifen for 5 years. Women who are postmenopausal, with a poorer prognosis, will receive an aromatase inhibitor for 5 years.
- All women who are premenopausal and are ER+ will receive tamoxifen.
- All women who have grade 3 tumours will receive chemotherapy.
- Women who are ER+ and have positive lymph nodes will receive combined treatment (hormone + chemotherapy).
- Women who are ER– and have 0 nodes will receive no treatment (exception to this is that 15% might get hormone therapy).
- Women who are ER– and have positive lymph nodes will receive chemotherapy (exception to this is that 15% might receive combined therapy).

Health-state utility values

The primary purpose of the economic model was to inform decision-making in a UK setting, given that treatment for breast cancer affects not only survival, but also quality of life, for example different types and stages of cancer are likely to be associated with differences in quality of life, as would different treatment options. Therefore, we have also sought to assess the impact on quality of life, through the incorporation of health-state utility weights, which have been combined with estimates of survival to estimate QALYs.

Recent guidance suggests that estimates of QALYs should ideally be based on generic health-state valuation methods using UK population tariffs.[100] Therefore, we conducted a focused search of the literature and other relevant sources such as the Harvard cost–utility database. We identified a number of studies reporting health-state utilities. In particular, we found a recent systematic review of breast cancer utility weights.[101] In their systematic review, 59 studies were identified

for review and nine studies included. Of the nine studies included, three were based on UK data.[102–104] In addition, the utility values used in the paper by Sorensen and colleagues[105] were based on a combination of UK and US data.[105]

It is difficult to determine how comprehensive this review is as, being available as a conference poster, the details provided on the literature searching are brief. The authors searched an appropriate selection of databases but the sensitivity of the search strategies used is unclear due to a lack of information. Missing information included whether MeSH terms were 'exploded' to include more specific terms, which Emtree terms were used in EMBASE, and how the terms were combined in the final search. From the information reported, one error was noted: 'breast neoplasms' was incorrectly described as a non-MeSH term.

Overall, the authors of the systematic review found considerable variability and inconsistency in the reported utility values. A selection of other studies eliciting health-state utilities was further identified. Overall, there was considerable variation in values and in definitions of health states; however, there is a general trend in the values reported in the literature. As would be expected, utilities decrease with increasing breast cancer severity and utilities are also found to be sensitive to treatment. For example, there is a general trend for those receiving chemotherapy to have lower utility values than those receiving hormone therapy, most likely due to the severity of the side effects of the respective treatments.

For the economic model, we have used the results reported in the systematic review of breast cancer utility weights.[101] Using this information, we defined utilities for each of the five risk profiles in the model. For example, risk profile state 1 assumes a utility state with a low value of 0.75 and a high value of 0.85 (based on the distribution of values from the systematic review). We adjusted these utility states to include a decrement for those women who will receive chemotherapy. This decrement is based on the percentage of women in each of the five severity states who would receive chemotherapy. For example, 24% of women in risk profile state 1 would receive chemotherapy. The chemotherapy decrement is based on information on patients' utilities for cancer treatments.[106] In their study, using the time trade-off method utilities for chemotherapy were estimated to be 0.74 from an actual health state estimated to be 0.94. All health-state utilities after treatment are assumed to be the same as the utilities defined before treatment without the chemotherapy decrement.

Utility values for risk profile states 3 and 4 are based on the health-state values in Tosteson and colleagues.[107] This is based on the value for regional cancer in the age group 50–59 years. The utility value for risk profile state 5 is based on the value provided for distant rather than regional cancer in the age group 50–59 years. Each of these values has also been reduced by the decrement factor for chemotherapy. To achieve the high values reported in *Table 38* for risk profile states 4 and 5 an additional 0.05 was added to the low value.

The values used in the base-case analysis are the low values reported in *Table 38*. Individuals in a 'no-cancer' state are assumed to have a health-state utility value of 0.80 in the base-case analysis.

Key assumptions of the economic model

This section provides a brief summary of the key assumptions made when developing the economic model.

Structural assumptions

The cycle length is assumed to be 6 months.

TABLE 38 Health-state utilities

| | | Managed | | | | Unmanaged | |
| | | On treatment | | After treatment | | | |
Severity	Percentage on chemotherapy	Low	High	Low	High	Low	High
1	0.240	0.71165	0.80654	0.8	0.95	0.8	0.95
2	0.759	0.59673	0.67629	0.8	0.95	0.8	0.95
3	0.769	0.52693	0.60376	0.63	0.68	0.8	0.95
4	0.991	0.49716	0.60807	0.63	0.68	0.8	0.95
5	1	0.39362	0.50394	0.5	0.55	0.8	0.95

It is assumed that, if individuals are invited to attend mammographic screening, they do in fact attend. This assumption may be too high, as approximately 75–80% of the normal population attend for breast screening.

Strategies compared are assumed to be homogeneous in that they do not change over time. More sophisticated strategies where the surveillance intervals and method of follow-up change over time have not been modelled.

Estimates of survival were based upon predictions derived from Adjuvant! Online and were grouped into five broad groupings based upon survival. This is a simplification of the different types of tumour that might occur, as well as how prognosis of untreated disease might change over time.

Parameter value assumptions – natural history assumptions

The incidence of IBTR and MCBC are assumed to be independent.

Incidence is assumed to have occurred at the point when a cancer could technically be identified.

The grade of IBTR does not have to be the same as that of the primary tumour but the grade of IBTR or MCBC does not have to change over time. There is some evidence to suggest that grade does not change. Should it occur as other evidence suggests, then, given the model structure, this would reduce the life expectancy of a woman. However, the impact on cost-effectiveness is unclear as it depends upon the likelihood of a tumour progressing to a higher grade, the speed of progression, the diagnostic performance of the surveillance regimen and the surveillance interval.

Estimates of survival are assumed to be independent of age (age-adjusted all-cause mortality is included as a separate model parameter). This may underestimate risks to younger women whose cancers might be more aggressive.

Treatments for IBTR and MCBC were based upon NICE guidelines and expert opinion.

If a cancer is not detected in a given cycle (6 months) then it is assumed that it can only advance one risk profile level. The likelihood of this occurring was estimated from the literature on doubling times.

Many of the estimates used to model natural history of disease are assumed to be constant over time. Some of these assumptions are not consistent with the observed data. However, the consensus of opinion for other parameters, for example probability of progressing to a risk profile

with a worse prognosis, is that they may decline over time. Allowing such probabilities to change over time would not greatly change costs but might be expected to increase QALYs over time for those strategies which have a better diagnostic performance.

Parameter value assumptions – diagnostic performance

Sensitivity and specificity for surveillance mammography and clinical follow-up were based upon expert opinion and assumed that it performed slightly better than surveillance mammography alone.

Sensitivity and specificity for clinical examination was based on clinical opinion. It was assumed that clinical examination has a lower sensitivity and specificity than reported in *Chapter 5*.

Parameter value assumptions – cost assumptions

Management packages previously prepared for UK guidance and HTAs have been used to estimate care, and hence costs. If treatment patterns have greatly altered in the last few years these data may not be applicable.

It is assumed that all women who have a breast cancer will incur the cost of a mastectomy. Obviously a woman who has had a previous mastectomy cannot have a further mastectomy on the same breast but the cost of a mastectomy has been used as a proxy for the cost of care such a woman would receive.

Parameter value assumptions – utilities assumptions

Data from different populations and elicited using different methods have been assumed to be sufficiently similar to the relevant UK population of women to be useful.

Utilities are assumed to reduce with increasing severity of disease and also on the use of chemotherapy. Other decrements to utility, for example complications of disease or treatment, are not modelled.

Presentation of results

The base-case analysis was run for a cohort of women (starting age in the model 57 years) with surveillance occurring once yearly. The starting age was chosen as this was the mean age of the women contributing to the analysis of data from the WMCIU Breast Cancer Registry, which was reported in *Chapter 6*. The model was run for different starting ages in further sensitivity analysis. The cycle length of the model is 6 months and cumulative costs and benefits are estimated over a maximum of 100 cycles, which is equivalent to a time horizon of 50 years. This time horizon was taken as a proxy for life expectancy of women treated for primary breast cancer. All costs are reported in 2008 pounds sterling and effectiveness in QALYS. A discount rate of 3.5% for costs and benefits was used following guidelines for NICE.[100] Results are presented as incremental cost per QALY gained. The modelling exercise will use a net benefit framework to combine cost and benefit estimates. The results of the analyses will be presented as point estimates of mean incremental costs, effects, incremental cost per QALY. This measure is a ratio of the difference in costs divided by the difference in effectiveness between two alternative strategies. These data can be interpreted as how much society would have to pay for an extra unit of effectiveness. Whether or not a more costly but more effective regimen is considered worthwhile depends upon society's willingness to pay for a QALY and, within England, the threshold adopted by NICE lies somewhere between £20,000 and £30,000.

Incremental cost per QALYs is a common way for presenting the results of an economic evaluation. They are, however, difficult to interpret when the choice is between several mutually exclusive options. In this circumstance the judgement can be informed by considering the net

benefit statistic. The regimen with the greatest net benefit at a given value for society's willingness to pay for a QALY is considered to be most cost-effective. The net benefit statistic itself is defined as:

$$NB_j = (QALY_j \times \lambda) - cost_j \qquad \text{[Equation 1]}$$

where NB = net benefit, $QALY_i$ = QALYs for intervention i, $cost_i$ = cost for intervention i, and λ = society's willingness to pay per QALY.

Intervention i would be chosen over intervention j when $NB_i > NB_j$.

Sensitivity analysis

We did not conduct probabilistic sensitivity analysis. The reason for this is that parameter values used are statistically imprecise and, as data are so limited, the model estimates may be unreliable. Therefore, the results of the economic evaluation should be interpreted cautiously and, at most, indicate situations where a particular method(s) of surveillance may be worthy of further consideration. Nevertheless, we conducted both one-way and multiway sensitivity analysis to assess how results may change as a consequence of plausible changes in parameter values. We also used deterministic sensitivity analysis to identify threshold values for key parameters. The methods used in the sensitivity analysis are described below.

Probability of developing IBTR or MCBC

We varied the probability of developing IBTR or MCBC in the sensitivity analysis from a low of 0.0030 [the lowest estimated 6-month cycle failure probability was for women who had a mastectomy and cumulatively had a risk of IBTR or MCBC of 0.0036 (*Table 27*)] to 0.0125 [the highest 6-month probability recurrence rate for IBTR and MCBC combined from the predicted HRs was 0.0125 (*Table 29*)].

Inflating the risk of death from cancer for people who are unmanaged

We also explored the effect of an increase in the risk of death for unmanaged individuals in sensitivity analyses. This was varied in the sensitivity analysis from the base-case assumption of 2.34 to a high of 2.916 (*Table 32* in the base-case model).

We repeated the same analysis in the IBTR model, varying the increase in the risk of death in unmanaged states from 2.33 to 2.916.

Changes to the risk of progressing to a higher risk profile

The consequences of changing the risk of unmanaged women progressing to higher-risk profiles was explored in both the base-case model and the IBTR model. The risk of progressing was altered from the base-case estimate of 0.1555 to 0.2623 in sensitivity analysis; 0.26 relates to a mean doubling time of 80 days and an estimated time of 300 days for a tumour to reach $2\,cm^3$ (*Table 33*). In addition, in a further sensitivity analysis the risk of progressing was further lowered form the base-case assumption, to a mean doubling time of 942 days. This equates to a risk of 0.0923 per 6-month cycle.

Sensitivity and specificity of the surveillance tests

The diagnostic performance of the surveillance tests (sensitivity and specificity) was varied in the base-case model for both high and low sensitivity and specificity values (reported in *Table 34*). This was undertaken in multiway sensitivity analysis, varying all the tests simultaneously.

Sensitivity analysis on costs

A range of sensitivity analyses on costs were performed. This included high treatment costs and surveillance costs. For example, the base-case model assumes that all women who receive hormone therapy receive tamoxifen. The consequences of this assumption were tested in sensitivity analyses. This involved re-estimating the model when all treatment costs were set to their highest estimates (highest cost for hormone and chemotherapy). In addition to treatment costs, higher surveillance costs were also incorporated into this sensitivity analysis. This included using the higher mammography cost (£77.80 as opposed to base-case assumption of £45.50) and also doubling the cost of an MRI. These cost estimates can be seen in *Tables 35* and *36*. The same analyses were conducted for the IBTR model.

The cost of all clinical examinations conducted either at the point of surveillance or in follow-up visits were varied from the base-case assumption that these clinical examinations would be carried out by a consultant grade, to the alternative assumption that these examinations were carried out by a non-consultant (*Table 35*). This analysis was conducted for both the base-case model and the IBTR model.

Sensitivity analysis on health-state utilities

Health-state utility values were also tested in a range of sensitivity analyses. This included replacing the base-case values for quality of life (assumed to be the low values reported in *Table 38*) with high estimates of quality of life (*Table 38*).

In addition, quality of life was further tested in both the base-case model and the IBTR model by varying the quality of life in unmanaged states. The base-case model assumes that women in unmanaged states have the same quality of life as women free of disease. This assumption is tested in sensitivity analysis by giving women in unmanaged states the same quality of life as women after treatment.

Age

The effect of age was tested in the sensitivity analysis with the base-case model and IBTR model, which we ran for a starting age of 40 years and a starting age of 70 years. This analysis was conducted as multiway sensitivity analysis with a range of values varied in the analysis. For the younger age group (starting age 40 years) this included high chemotherapy and high hormone therapy costs (*Table 36*), high cancer incidence (0.0152, *Table 29*) and a short doubling time (0.2623, *Table 33*). In addition, for this age group, a further multiway analysis was conducted, repeating the analysis above, with the addition of the high inflation factor for unmanaged states (2.916, *Table 32*).

For a starting age of 70 years, sensitivity analysis was conducted for the base-case model and IBTR model using the new starting age of 70 years and the low hazard rate (0.0018, *Table 29*). All of the other variables were assumed to be as the base-case assumptions.

Results

Base-case results

Results for women who received BCS or mastectomy for their primary cancer

Tables 39 and *40* report the results of the base-case analyses for the average women treated for their primary breast cancer with BCS or with a mastectomy. These data can be used to inform

TABLE 39 Results of the base-case analysis for women treated for their primary cancer with BCS

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	1033	12.925		257,459	12	386,705	13
Mammography alone	1970	13.123	4727	260,484	1	391,711	1
Mammography + clinical	3396	13.129	236,826	259,178	8	390,465	7
MRI + clinical	6499	13.139	297,848	256,283	13	387,675	12
18-month interval							
No surveillance	1033	12.925		257,459	12	386,705	13
Mammography alone	1722	13.105	3811	260,385	2	391,438	2
Mammography + clinical	2743	13.114	118,455	259,536	6	390,675	5
MRI + clinical	4969	13.130	142,331	257,623	11	388,919	11
24-month interval							
No surveillance	1033	12.925		257,459	12	386,705	13
Mammography alone	1587	13.089	3366	260,197	3	391,089	3
Mammography + clinical	2408	13.100	78,167	259,586	5	390,583	6
MRI + clinical	4200	13.120	90,382	258,191	10	389,387	10
36-month interval							
No surveillance	1033	12.925		257,459	12	386,705	14
Mammography alone	1498	13.075	3099	259,994	4	390,740	4
Mammography + clinical	2201	13.086	59,607	259,528	7	390,392	8
MRI + clinical	3734	13.109	66,789	258,453	9	389,547	9

judgements about what would be the single best regimen for the NHS to adopt for all women who had previously been treated with BCS or all women who had previously been treated with mastectomy. For both populations the results are shown for a range of surveillance intervals ranging from 12 months to 36 months. The costs and outcomes for the 'no surveillance' option are the same regardless of the surveillance interval. For the other surveillance regimens, both costs and QALYs fall as the surveillance interval increases. However, for each surveillance regimen the reduction in QALYs is more than compensated for by a reduction in cost. This is illustrated by the reduction in the incremental cost per QALY reported for each regimen as the surveillance interval increases. For example, for women who had received BCS the incremental cost per QALY for mammography alone compared with 'no surveillance' is £4727 for a 12-month surveillance regimen and £3811 for an 18-month regimen. Similarly, for a 12-month surveillance regimen the incremental cost per QALY for mammography and clinical follow-up alone compared with mammography is £236,826. For an 18-month surveillance interval the incremental cost per QALY falls to £118,455.

The results of the two sets of analyses reported in *Tables 39* and *40* are very similar. As would be expected, the no surveillance regimen is least costly but also least effective. Whether or not a more costly but more effective regimen is considered worthwhile depends upon society's willingness to pay for a QALY. Within England, the threshold adopted by NICE lies somewhere between £20,000 and £30,000, and, as shown in *Tables 39* and *40*, only one regimen, mammography alone, is associated with an incremental cost per QALY below £20,000.

TABLE 40 Results of the base-case analysis for women treated for their primary cancer with mastectomy

				Net benefits (£)			
Regimen	Cost (£)	QALY	ICER (£)	λ = 20,000	Rank	λ = 30,000	Rank
12-month interval							
No surveillance	1012	12.938		257,753	8	387,136	10
Mammography alone	1927	13.127	4861	260,603	1	391,868	1
Mammography + clinical	3360	13.132	250,230	259,285	8	390,608	7
18-month interval							
No surveillance	1012	12.938		257,753	8	387,136	9
Mammography alone	1680	13.110	3885	260,521	2	391,621	2
Mammography + clinical	2705	13.118	125,115	259,660	7	390,842	5
24-month interval							
No surveillance	1012	12.938		257,753	8	387,136	10
Mammography alone	1545	13.095	3407	260,349	3	391,296	3
Mammography + clinical	2369	13.105	82,525	259,725	5	390,772	6
36-month interval							
No surveillance	1012	12.938		257,753	8	387,136	10
Mammography alone	1457	13.081	3117	260,160	4	390,969	4
Mammography + clinical	2161	13.092	62,899	259,680	6	390,600	8

Incremental cost per QALYs, as reported in *Tables 39* and *40*, can be difficult to interpret when the choice is between several different options (e.g. in *Table 39* there are 13 different regimens and it is not immediately obvious which option might be considered most cost-effective). Therefore, we used the net benefit statistic to compare regimens. When society's willingness to pay for a QALY is £20,000, the regimen that is associated with the highest net benefit is mammography alone every year (*Tables 39* and *40*). When the threshold was increased to £30,000 mammography only had the greatest net benefit. Regardless of the surveillance interval, mammography alone had the highest net benefits and the regimen with the lowest net benefit was always no surveillance.

In *Table 39* the impact of substituting a more effective but more costly surveillance technology (MRI) for mammography was considered. Regardless of the surveillance interval, this regimen was associated with a net benefit greater than that of the no surveillance regimen but less than that of all of the other regimens.

Modelling IBTR alone

The analyses reported in *Tables 39* and *40* made the assumption that the consequences of an IBTR are the same as those of an otherwise identical contralateral recurrence. However, the analyses reported in *Chapter 6* suggest that the mortality associated with IBTR is substantially higher than that associated with an otherwise identical recurrence in the contralateral breast. In this analysis this increased risk of death from IBTR is modelled (*Table 41*).

In these analyses the regimen mammography alone has an incremental cost per QALY compared with 'no surveillance' of < £4000 and the highest net benefit regardless of the surveillance interval. Mammography alone at 12 months has a marginally higher net benefit than mammography alone at 24 months for both a £20,000 and a £30,000 threshold for society's willingness to pay for a QALY.

TABLE 41 Ipsilateral breast tumour recurrence has a substantial higher risk of death than MCBC

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£) λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	978	12.830		255,620	12	383,920	13
Mammography alone	1956	13.076	3973	259,565	1	390,326	1
Mammography + clinical	3384	13.084	177,150	258,298	8	389,139	5
MRI + clinical	6491	13.098	216,537	255,478	13	386,463	12
18-month interval							
GP only	978	12.830		255,620	12	383,920	13
Mammography alone	1703	13.053	3247	259,359	2	389,890	2
Mammography + clinical	2727	13.064	92,265	258,557	5	389,198	4
MRI + clinical	4958	13.085	108,007	256,739	11	387,587	11
24-month interval							
GP only	978	12.830		255,620	12	383,920	13
Mammography alone	1563	13.032	2887	259,084	3	389,407	3
Mammography + clinical	2387	13.046	62,482	258,523	6	388,978	6
MRI + clinical	4185	13.071	70,315	257,237	10	387,947	10
36-month interval							
GP only	978	12.830		255,620	12	383,920	13
Mammography alone	1468	13.014	2664	258,808	4	388,946	7
Mammography + clinical	2175	13.028	48,551	258,393	7	388,676	8
MRI + clinical	3716	13.058	52,811	257,435	9	388,010	9

Sensitivity analyses

We conducted a range of different sensitivity analyses, as described above in *Presentation of results*. As the results for the analyses for women who received BCS for their primary cancer are similar to those obtained when we consider women who received a mastectomy for their primary cancer we present sensitivity analyses solely for the scenario where women received BCS for their primary cancer. However, we also report selected analyses for a model that considers IBTR alone.

Sensitivity analysis around the breast-conserving model
Probability of developing cancer

Figures 26–29 illustrate the impact on incremental cost per QALYs as the incidence of cancer increases. In each figure, three lines are shown:

1. The incremental cost per QALY of mammography alone compared with no surveillance. This line can be used to inform the question: is it worth adopting the more effective but more costly mammography alone follow-up in place of the less costly and less effective no surveillance regimen?
2. The incremental cost per QALY of mammography plus clinical follow-up compared with mammography alone. This line can be used to inform the question: is it worth adopting the more effective but more costly mammography plus clinical follow-up in place of the less costly and less effective mammography alone regimen?
3. The incremental cost per QALY of MRI plus clinical follow-up compared with mammography plus clinical follow-up. This line can be used to inform the question: is it
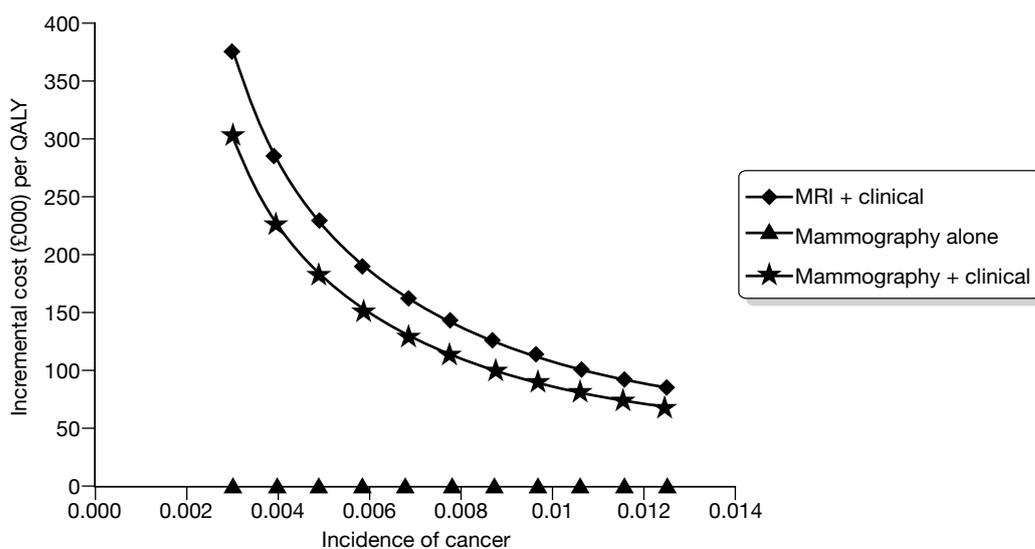
FIGURE 26 Incremental cost per QALYs for the different surveillance regimens at a 12-month surveillance interval.
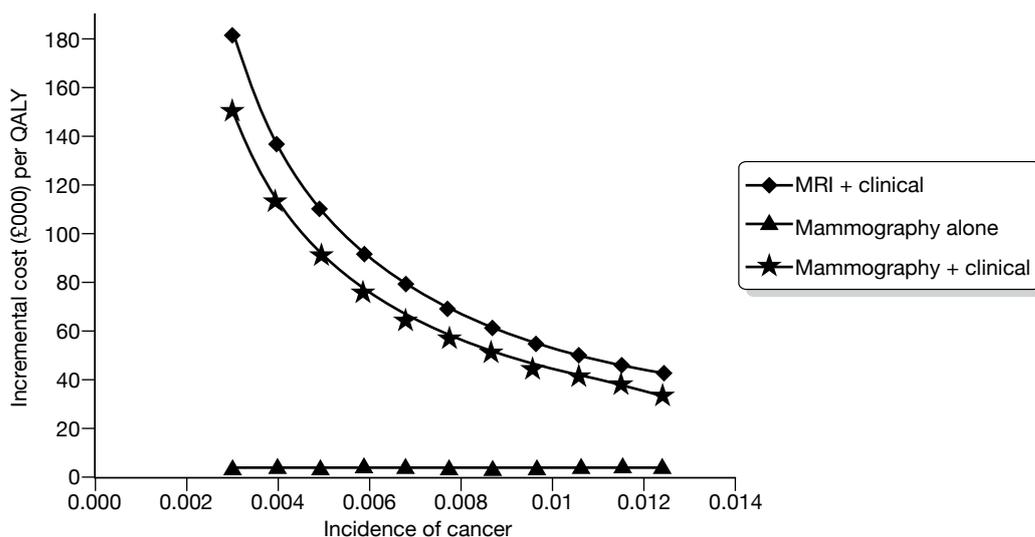
FIGURE 27 Incremental cost per QALYs for the different surveillance regimens at an 18-month surveillance interval.

worth adopting the more effective but more costly MRI plus clinical follow-up in place of the less costly and less effective mammography plus clinical follow-up regimen?

The results of the analysis shown in these figures suggest that:

■ At all screening intervals considered some form of active surveillance might be considered cost-effective.
■ Should the incidence of IBTR and MCBC increase towards the upper values of incidence considered, which are typical of those we might expect for higher risk women (e.g. those whose primary cancers were of higher grade, who were younger than 50 years and who had lymph node involvement), a regimen of clinical follow-up and mammography is more likely to be worthwhile. Furthermore, when the surveillance interval is 24 months the incremental
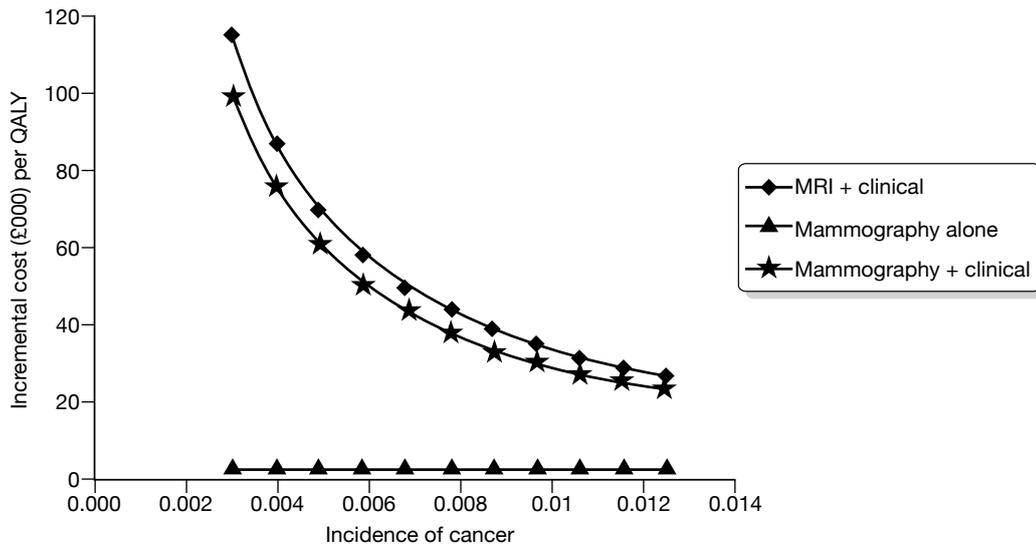
FIGURE 28 Incremental cost per QALYs for the different surveillance regimens at a 24-month surveillance interval.
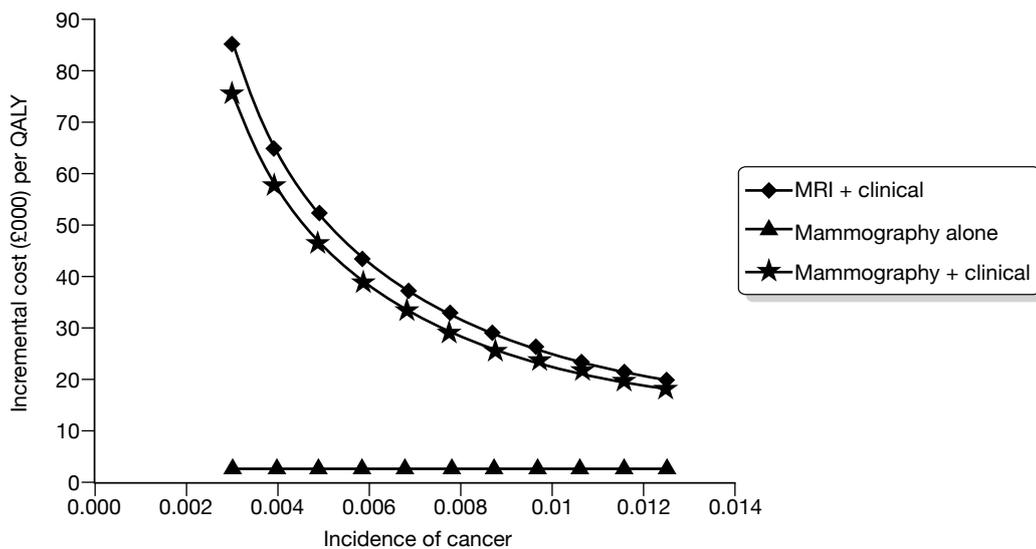
FIGURE 29 Incremental cost per QALYs for the different surveillance regimens at a 36-month surveillance interval.

cost per QALY compared with mammography alone approaches £30,000. At a surveillance interval of 36 months, it is approximately £25,000.

■ As the screening interval and risk of IBTR and MCBC increases towards 36 months, it becomes more likely that a more costly but more effective surveillance intervention (in this analysis typified by MRI plus clinical follow-up) might be worthwhile.

Inflating the risk of death from untreated cancer

Sensitivity analysis was conducted to test the effect of inflating the risk of death for women who are unmanaged for cancer. In the sensitivity analysis the increased risk of death from cancer in unmanaged states was inflated from the base-case risk of 2.34 to a high of 2.196 (*Table 42*). The results of this analysis were broadly similar to the base-case analysis presented in *Table 39*. We conducted this sensitivity analysis for both the base-case model and the IBTR model.

TABLE 42 Increasing the risk of death for unmanaged disease

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
GP only	1014	12.898		256,939	13	385,915	13
Mammography alone	1967	13.120	4278	260,440	1	391,644	1
Mammography + clinical	3394	13.127	217,826	259,145	8	390,414	7
MRI + clinical	6498	13.138	274,030	256,267	14	387,649	12
18-month interval							
GP only	1014	12.898		256,939	12	385,915	13
Mammography alone	1718	13.101	3451	260,312	2	391,326	2
Mammography + clinical	2740	13.111	108,767	259,477	6	390,586	4
MRI + clinical	4967	13.128	130,986	257,590	11	388,869	11
24-month interval							
GP only	1014	12.898		256,939	13	385,915	13
Mammography alone	1581	13.084	3045	260,096	3	390,935	3
Mammography + clinical	2403	13.095	71,562	259,504	5	390,457	6
MRI + clinical	4197	13.117	83,055	258,142	10	389,312	10
36-month interval							
GP only	1014	12.898		256,939	13	385,915	13
Mammography alone	1490	13.068	2796	259,867	4	390,546	5
Mammography + clinical	2194	13.081	54,384	259,422	7	390,231	8
MRI + clinical	3730	13.106	61,238	258,388	9	389,447	9

Changes to the probability of progressing to a more serious risk profile

Table 43 reports the impact of increasing the speed that an untreated cancer progresses to a risk profile with a worse prognosis. As would be expected the higher the probability of progression (which would be analogous to a shorter doubling time of a tumour) the more likely earlier and more intensive follow-up becomes. Nevertheless, in this one-way sensitivity analysis none of the options, other than mammography alone, is associated with incremental costs per QALY approaching a value that society typically might be willing to pay.

Changes to the sensitivity and specificity of the tests

Tables 44 and *45* show multiway sensitivity analysis on the diagnostic performance of the surveillance tests. Again, changes in the sensitivities and specificities alone do not greatly alter the estimated cost-effectiveness of the different regimens.

Changes to costs of tests and treatments

Sensitivity analysis was also performed on costs. This included a high treatment cost and high surveillance cost sensitivity analysis. This involved re-estimating the model when all treatment costs were set to their highest estimates (highest cost for hormone and chemotherapy). In addition to treatment costs, higher surveillance costs were also incorporated into this sensitivity analysis. This included using the higher mammography cost (£78 as opposed to base-case assumption of £45.50) and also doubling the cost of an MRI. These cost estimates can be seen in *Table 46*. The same analyses were conducted for the IBTR model (and are reported in the next subsection).

TABLE 43 The impact of changing the probability of progressing to a higher risk profile

Surveillance interval	Regimen	ICER at low and high probability of increasing to next risk profile per cycle:		
		0.0923	0.1555	0.2623
12 months	No surveillance			
	Mammography alone	6580	4727	3679
	Mammography + clinical	389,207	236,826	137,745
	MRI + clinical	487,420	297,848	170,226
18 months	No surveillance			
	Mammography alone	5168	3811	3093
	Mammography + clinical	193,537	118,455	71,767
	MRI + clinical	235,502	142,331	83,040
24 months	No surveillance			
	Mammography alone	4456	3366	2833
	Mammography + clinical	125,343	78,167	49,644
	MRI + clinical	148,299	90,382	54,714
36 months	No surveillance			
	Mammography alone	4014	3099	2690
	Mammography + clinical	93,489	59,607	39,604
	MRI + clinical	107,873	66,789	42,079

TABLE 44 High sensitivity and specificity values

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	1058	12.958		258,097	11	387,674	13
Mammography alone	1944	13.126	5280	260,568	1	391,823	1
Mammography + clinical	3343	13.132	211,875	259,300	8	390,622	8
MRI + clinical	6390	13.141	338,553	256,433	13	387,845	12
18-month interval							
No surveillance	1058	12.958		258,097	11	387,674	13
Mammography alone	1690	13.110	4150	260,511	2	391,612	2
Mammography + clinical	2676	13.120	104,218	259,715	7	390,910	5
MRI + clinical	4826	13.133	159,306	257,835	12	389,165	11
24-month interval							
No surveillance	1058	12.958		258,097	11	387,674	13
Mammography alone	1554	13.096	3597	260,360	3	391,317	3
Mammography + clinical	2335	13.107	67,680	259,810	5	390,882	6
MRI + clinical	4040	13.124	99,707	258,447	10	389,691	10
36-month interval							
No surveillance	1058	12.958		258,097	11	387,674	13
Mammography alone	1466	13.083	3263	260,189	4	391,017	4
Mammography + clinical	2126	13.096	50,836	259,789	6	390,746	7
MRI + clinical	3566	13.116	72,694	258,745	9	389,900	9

TABLE 45 Low sensitivity and specificity values

| Regimen | Cost (£) | QALY | ICER (£) | Net benefits (£) | | | |
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	1061	12.900		256,942	12	385,944	13
Mammography alone	2023	13.121	4365	260,388	1	391,594	1
Mammography + clinical	3467	13.125	342,589	259,029	8	390,277	6
MRI + clinical	6600	13.128	859,244	255,969	13	387,253	12
18-month interval							
No surveillance	1061	12.900		256,942	12	385,944	13
Mammography alone	1792	13.102	3622	260,246	2	391,264	2
Mammography + clinical	2835	13.108	173,779	259,323	6	390,401	5
MRI + clinical	5094	13.113	425,796	257,170	11	388,301	11
24-month interval							
No surveillance	1061	12.900		256,942	12	385,944	13
Mammography alone	1664	13.084	3270	260,026	3	390,870	3
Mammography + clinical	2508	13.092	116,098	259,327	5	390,244	7
MRI + clinical	4331	13.098	278,691	257,634	10	388,617	10
36-month interval							
No surveillance	1061	12.900		256,942	12	385,944	13
Mammography alone	1577	13.069	3063	259,796	4	390,483	4
Mammography + clinical	2303	13.077	89,497	259,232	7	390,000	8
MRI + clinical	3866	13.084	211,068	257,818	9	388,660	9

In addition, *Table 47* shows sensitivity analysis in which the cost of a clinical examination is priced at the consultant and non-consultant rate and the effect on the incremental cost per QALYs. Although the changes are minor, adopting a lower cost for a clinical examination makes the mammography alone regimen marginally less cost-effective compared with 'no surveillance'. This is because the lower cost is also incurred for all clinical examinations, including those during follow-up for those with IBTR or MCBC.

Changes to utility estimates used

The analysis presented in *Table 48* is based on the high estimates of quality of life reported in *Table 38*. The results suggest that at a willingness-to-pay threshold of £20,000 the regimen with the highest net benefit is likely to be mammography alone at 12-month surveillance intervals, followed by mammography alone at 18-, then 24- and then 36-month intervals. At a willingness-to-pay threshold of £30,000 the ordering is very similar with the exception that mammography plus clinical examination has the fourth highest net benefit at a willingness-to-pay threshold of £30,000.

In addition to sensitivity analysis on higher quality-of-life values, we conducted further sensitivity analyses to test the base-case assumption that women in unmanaged states have the same quality of life as women who are disease free. We tested this assumption by giving all women in unmanaged states the same utility as women who had been treated for IBTR or MCBC. These results are presented in *Table 49*. Decreasing the quality of life of women in unmanaged states has no appreciable effect on the analysis presented above for a threshold value of £20,000 or £30,000.

TABLE 46 High-cost sensitivity analysis

				Net benefits (£)			
Regimen	Cost (£)	QALY	ICER (£)	λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	1704	12.925		256,787	9	386,033	10
Mammography alone	3940	13.123	11,284	258,514	3	389,741	1
Mammography + clinical	5384	13.129	239,765	257,191	8	388,478	8
MRI + clinical	11826	13.139	618,286	250,957	13	382,348	13
18-month interval							
No surveillance	1704	12.925		256,787	9	386,033	10
Mammography alone	3483	13.105	9842	258,623	1	389,676	2
Mammography + clinical	4532	13.114	121,600	257,747	7	388,887	6
MRI + clinical	9173	13.130	296,783	253,419	12	384,715	12
24-month interval							
No surveillance	1704	12.925		256,787	9	386,033	10
Mammography alone	3219	13.089	9199	258,565	2	389,458	3
Mammography + clinical	4075	13.100	81,481	257,920	6	388,917	5
MRI + clinical	7826	13.120	189,286	254,565	11	385,760	11
36-month interval							
No surveillance	1704	12.925		256,787	9	386,033	10
Mammography alone	3034	13.075	8861	258,459	4	389,205	4
Mammography + clinical	3777	13.086	63,077	257,951	5	388,815	7
MRI + clinical	7,001	13.109	140,417	255,186	10	386,280	9

TABLE 47 Consultant and non-consultant cost of clinical examinations

		ICER at low and high clinical examination cost (£):	
Surveillance interval	Regimen	65	86
12 months	No surveillance		
	Mammography alone	4945	4727
	Mammography + clinical	178,716	236,826
	MRI + clinical	297,829	297,848
18 months	No surveillance		
	Mammography alone	4057	3811
	Mammography + clinical	89,362	118,455
	MRI + clinical	142,296	142,331
24 months	No surveillance		
	Mammography alone	3644	3366
	Mammography + clinical	59,002	78,167
	MRI + clinical	90,339	90,382
36 months	No surveillance		
	Mammography alone	3410	3099
	Mammography + clinical	45,043	59,607
	MRI + clinical	66,741	66,789

TABLE 48 Sensitivity analysis using high estimates of quality of life

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	1033	13.080		260,573	12	391,376	13
Mammography alone	1970	13.320	3902	264,436	1	397,638	1
Mammography + clinical	3396	13.328	183,571	263,165	8	396,445	5
MRI + clinical	6499	13.341	231,932	260,329	9	393,743	12
18-month interval							
No surveillance	1033	13.080		260,573		391,376	13
Mammography alone	1722	13.298	3164	264,237	2	397,216	2
Mammography + clinical	2743	13.309	91,801	263,438	5	396,529	4
MRI + clinical	4969	13.329	109,808	261,618	11	394,911	11
24-month interval							
No surveillance	1033	13.080		260,573	12	391,376	13
Mammography alone	1587	13.277	2813	263,958	3	396,731	3
Mammography + clinical	2408	13.291	61,015	263,407	6	396,314	6
MRI + clinical	4200	13.316	69,854	262,128	10	395,292	10
36-month interval							
No surveillance	1033	13.080		260,573	12	391,376	13
Mammography alone	1498	13.259	2606	263,676	4	396,263	7
Mammography + clinical	2201	13.274	46,960	263,272	7	396,009	8
MRI + clinical	3734	13.303	51,938	262,329	13	395,361	9

Exploration of the impact of age at the time surveillance starts

Table 50 reports the results of sensitivity analysis based on a starting age in the model of 40 years old. This table not only reports multiway sensitivity analysis for a starting age of 40 years, but also includes high chemotherapy costs and high hormone therapy costs (*Table 36*). In addition, a higher incidence rate for cancer is used in this model (0.0152, *Table 29*) and high probability of moving to the next risk profile. This analysis was conducted for surveillance intervals ranging from 12 to 36 months. In this analysis, the option with the highest net benefit is mammography alone at a surveillance interval of 12 months for a willingness-to-pay threshold of £20,000 per QALY. At a higher willingness-to-pay threshold of £30,000 per QALY, MRI plus clinical examination at a surveillance interval of 12 months has the highest net benefit. The second highest net benefit at a threshold of £20,000 and £30,000 is mammography and clinical examination at 12-month surveillance intervals.

In addition to a starting age of 40 years old, sensitivity analysis was also conducted on a higher starting age. In this model all parameters are assumed to be as the base-case assumptions with two differences: (1) starting age is 70 years old and (2) the incidence of cancer is based on the lowest hazard estimates (*Table 29*). The results of this analysis are presented in *Table 51*. At a willingness-to-pay threshold of £20,000 per QALY, the test with the highest net benefit is mammography alone at a 36-month interval. At a willingness-to-pay threshold of £30,000, the regimen with the highest net benefit is mammography alone at intervals of 24 months.

TABLE 49 Sensitivity analysis on quality of life in unmanaged states: breast-conserving model

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	1033	12.880		256,573	12	385,377	13
Mammography alone	1970	13.122	3868	260,478	1	391,702	1
Mammography + clinical	3396	13.129	230,558	259,175	8	390,461	6
MRI + clinical	6499	13.139	293,795	256,283	13	387,674	12
18-month interval							
No surveillance	1033	12.880		256,573	12	385,377	13
Mammography alone	1722	13.087	3075	260,021	3	390,892	3
Mammography + clinical	2743	13.098	112,416	259,227	7	390,211	8
MRI + clinical	4969	13.119	137,827	257,418	11	388,612	11
24-month interval							
No surveillance	1033	12.880		256,573	12	385,377	13
Mammography alone	1587	13.087	2679	260,155	2	391,027	2
Mammography + clinical	2408	13.098	72,359	259,561	5	390,546	5
MRI + clinical	4200	13.119	85,807	258,188	10	389,381	10
36-month interval							
No surveillance	1033	12.880	0	256,573	12	385,377	13
Mammography alone	1498	13.071	2435	259,927	4	390,640	4
Mammography + clinical	2201	13.084	53,905	259,485	6	390,328	7
MRI + clinical	3734	13.109	62,168	258,445	9	389,535	9

TABLE 50 Sensitivity analysis for a starting age of 40 years: breast-conserving model

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	5097	14.592		286,742	13	432,661	13
Mammography alone	11,885	16.364	3831	315,392	1	479,031	3
Mammography + clinical	13,332	16.428	22,596	315,226	2	479,505	2
MRI + clinical	16,389	16.540	27,173	314,419	3	479,823	1
18-month interval							
No surveillance	5097	14.592		286,742	13	432,661	13
Mammography alone	11,308	16.183	3904	312,348	7	474,175	7
Mammography + clinical	12,457	16.272	12,929	312,976	5	475,692	6
MRI + clinical	14,850	16.437	14,459	313,893	4	478,265	4
24-month interval							
No surveillance	5097	14.592		286,742	13	432,661	13
Mammography alone	10,829	16.019	4016	309,558	10	469,751	10
Mammography + clinical	11,853	16.124	9769	310,630	9	471,871	9
MRI + clinical	13,966	16.328	10,350	312,600	6	475,883	5

TABLE 50 Sensitivity analysis for a starting age of 40 years: breast-conserving model *(continued)*

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£) λ = £20,000	Rank	λ = £30,000	Rank
36-month interval							
No surveillance	5097	14.592		286,742	13	432,661	13
Mammography alone	10,404	15.875	4135	307,100	12	465,852	12
Mammography + clinical	11,363	15.989	8414	308,422	11	468,314	11
MRI + clinical	13,337	16.219	8573	311,053	8	473,248	8

TABLE 51 Sensitivity analysis for a starting age of 70 years: breast-conserving model

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£) λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	541	9.068		180,828		271,512	6
Mammography alone	1047	9.100	16,182	180,947	4	271,944	4
Mammography + clinical	2082	9.101	880,839	179,935	9	270,944	9
MRI + clinical	4340	9.103	1,093,357	177,719	12	268,749	13
18-month interval							
No surveillance	541	9.068		180,828	5	271,512	6
Mammography alone	867	9.096	11,701	181,060	3	272,023	2
Mammography + clinical	1603	9.098	451,156	180,357	8	271,337	8
MRI + clinical	3211	9.101	529,198	178,810	11	269,820	12
24-month interval							
No surveillance	541	9.068		180,828	5	271,512	6
Mammography alone	773	9.093	9331	181,093	2	272,026	1
Mammography + clinical	1359	9.095	305,494	180,546	7	271,498	7
MRI + clinical	2644	9.099	342,629	179,336	10	270,326	11
36-month interval							
No surveillance	541	9.068		180,828	5	271,512	6
Mammography alone	713	9.091	7751	181,100	1	272,006	3
Mammography + clinical	1210	9.093	238,858	180,644	6	271,571	5
MRI + clinical	2302	9.097	258,696	179,636	10	270,606	10

Sensitivity analysis around model considering IBTR only
Probability of developing cancer

Figures 30–33 report the impact of increasing the incidence of IBTR only. In these analyses, the impact on costs and QALYs or MCBC is not considered. As described earlier, IBTR has a much worse prognosis than MCBC. As would be expected, as incidence increases the incremental cost per QALYs fall when we compare a more effective but more costly surveillance regimen with the next most costly and effective. For mammographic and clinical follow-up the incremental cost per QALY compared with mammography alone begins to fall below £30,000 once the incidence
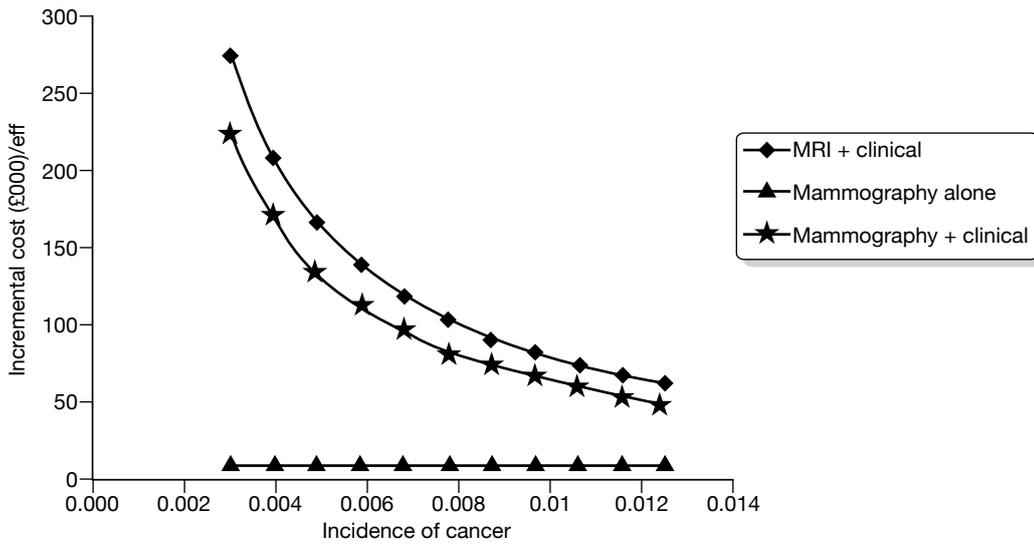
FIGURE 30 Incremental cost per QALYs for the different surveillance regimens at a 12-month surveillance interval.
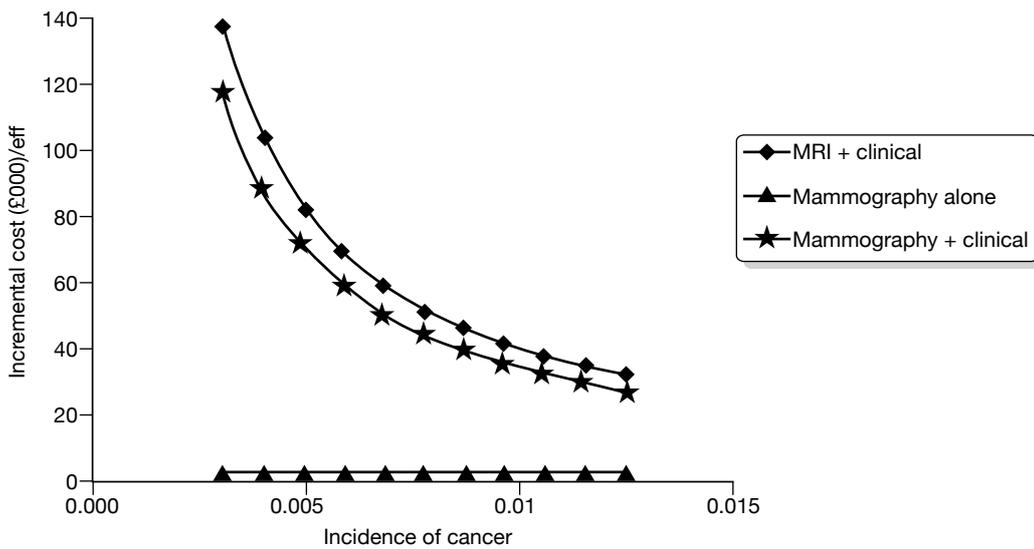
FIGURE 31 Incremental cost per QALYs for the different surveillance regimens at an 18-month surveillance interval.

of disease exceeds 0.00775 every 6 months and the surveillance interval is 24 months or longer. When the surveillance interval reaches 36 months, the adoption of a more effective but more costly regimen (again typified by MRI plus clinical follow-up) may be cost-effective once the incidence per cycle exceeds 0.0068.

Inflating the risk of death from untreated cancer
In this sensitivity analysis, the increased risk of death from cancer in unmanaged states was inflated from the base-case risk of 2.34 to a high of 2.196 (*Table 52*). The results of this analysis were broadly similar to the base-case analysis presented in *Table 41*.
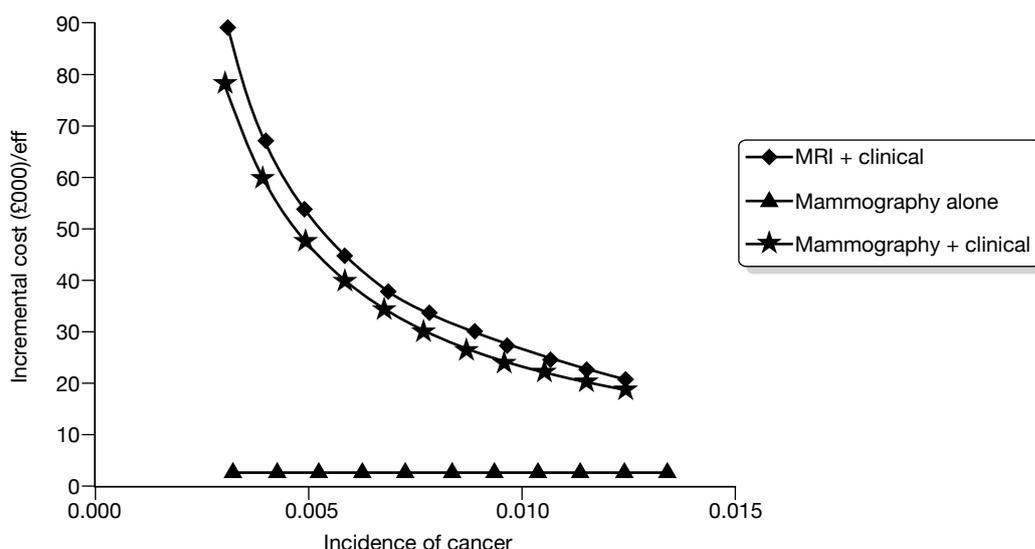
FIGURE 32 Incremental cost per QALYs for the different surveillance regimens at a 24-month surveillance interval.
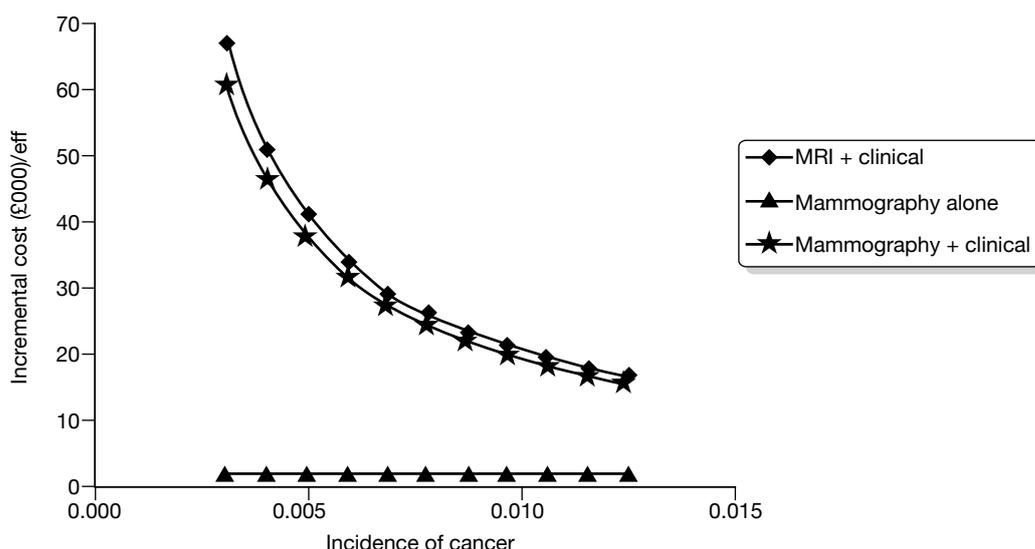
FIGURE 33 Incremental cost per QALYs for the different surveillance regimens at a 36-month surveillance interval.

Changes to the probability of progressing to a more serious risk profile

Table 53 reports the impact of increasing the speed that an untreated cancer progresses to a risk profile with a worse prognosis. The results of this analysis are similar to those reported above and it is unlikely that changes in this variable alone will result in any regimen other than mammography alone having an incremental cost per QALY that society might be willing to pay.

Changes to costs of tests and treatments

Table 54 shows a high treatment cost and high surveillance cost sensitivity analysis for the IBTR model. Again, the results of this sensitivity analysis are broadly similar to those reported in *Table 41*.

TABLE 52 Increasing the risk of death for unmanaged disease

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
GP only	956	12.798		255,010	13	382,994	12
Mammography alone	1952	13.072	3634	259,494	1	390,217	1
Mammography + clinical	3381	13.081	160,846	258,243	7	389,054	4
MRI + clinical	6490	13.097	196,526	255,450	12	386,420	11
18-month interval							
GP only	956	12.798		255,010	13	382,994	12
Mammography alone	1696	13.047	2973	259,243	2	389,713	2
Mammography + clinical	2721	13.059	83,817	258,462	5	389,054	4
MRI + clinical	4955	13.082	97,976	256,685	11	387,504	10
24-month interval							
GP only	956	12.798		255,010	13	382,994	12
Mammography alone	1553	13.024	2642	258,928	3	389,168	3
Mammography + clinical	2379	13.039	56,792	258,392	6	388,778	5
MRI + clinical	4180	13.067	63,721	257,156	10	387,825	9
36-month interval							
GP only	956	12.798		255,010	13	382,994	12
Mammography alone	1456	13.004	2433	258,615	4	388,651	6
Mammography + clinical	2164	13.020	44,151	258,228	8	388,424	7
MRI + clinical	3710	13.052	47,805	257,329	9	387,848	8

TABLE 53 The impact of changing the probability of progressing to a higher risk profile

Surveillance interval	Regimen	ICER at low and high probability of increasing to next risk profile per cycle:	
		0.1555	0.2623
12 months	No surveillance		
	Mammography alone	3973	3231
	Mammography + clinical	177,150	110,112
	MRI + clinical	216,537	131,811
18 months	No surveillance		
	Mammography alone	3247	2523
	Mammography + clinical	92,265	42,743
	MRI + clinical	108,007	44973.0307
24 months	No surveillance		
	Mammography alone	2887	2523
	Mammography + clinical	62,482	42,743
	MRI + clinical	70,315	44,973
36 months	No surveillance		
	Mammography alone	2664	2391
	Mammography + clinical	48,551	34,901
	MRI + clinical	52,811	34,980

TABLE 54 Ipsilateral breast tumour recurrence model: high costs

Regimen	Cost (£)	QALY	ICER (£)	Net benefits (£)			
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	1578	12.830		255,021	9	383,320	11
Mammography alone	3869	13.076	9309	257,652	2	388,413	1
Mammography + clinical	5317	13.084	179,674	256,365	8	387,206	6
MRI + clinical	11,768	13.098	449,596	250,202	13	381,186	12
18-month interval							
No surveillance	1578	12.830		255,021	9	383,320	11
Mammography alone	3400	13.053	8164	257,662	1	388,193	2
Mammography + clinical	4454	13.064	95,002	256,830	7	387,471	4
MRI + clinical	9107	13.085	225,253	252,590	12	383,438	10
24-month interval							
No surveillance	1578	12.830		255,021	9	383,320	11
Mammography alone	3124	13.032	7638	257,523	3	387,846	3
Mammography + clinical	3987	13.046	65,386	256,924	5	387,379	5
MRI + clinical	7752	13.071	147,255	253,670	11	384,381	9
36-month interval							
No surveillance	1578	12.830		255,021	9	383,320	11
Mammography alone	2929	13.014	7345	257,348	4	387,486	3
Mammography + clinical	3679	13.028	51,600	256,888	6	387,172	7
MRI + clinical	6919	13.058	110,989	254,232	10	384,808	8

In addition, *Table 55* shows sensitivity analysis in which the cost of a clinical examination is priced at the consultant and non-consultant rate. Although the incremental cost per QALYs changes, none is of sufficient magnitude to change conclusions.

Changes to utility estimates used

We tested the base-case assumption that women in unmanaged states have the same quality of life as women who are disease free (*Table 56*). In this analysis, all women in unmanaged states had the same utility as women who had been treated for IBTR or MCBC. A similar pattern of results is observed in the IBTR model sensitivity analysis as was observed in the breast-conserving model sensitivity analysis.

Exploration of the impact of age at the time surveillance starts

Table 57 reports the results of sensitivity analysis based on a starting age of 40 years old in the IBTR model. This table reports multiway sensitivity analysis for starting age 40 years, and includes the high chemotherapy costs and high hormone therapy costs (*Table 36*). In addition, the higher incidence rate for cancer is used in this model (0.0152, *Table 29*) and a short doubling time. This analysis was conducted for surveillance intervals ranging from 12 to 36 months.

TABLE 55 Consultant and non-consultant cost of clinical examinations

		ICER at low and high clinical examination cost (£):	
Surveillance interval	Regimen	65	86
12 months	No surveillance		
	Mammography alone	4148	3973
	Mammography + clinical	133,736	177,150
	MRI + clinical	216,515	216,537
18 months	No surveillance		
	Mammography alone	3446	3247
	Mammography + clinical	69,664	92,265
	MRI + clinical	107,973	108,007
24 months	No surveillance		
	Mammography alone	3113	2887
	Mammography + clinical	47,228	62,482
	MRI + clinical	70,274	70,315
36 months	No surveillance		
	Mammography alone	2919	2664
	Mammography + clinical	36,756	48,551
	MRI + clinical	52,766	52,811

TABLE 56 Sensitivity analysis on quality of life in unmanaged states: IBTR model

				Net benefits			
Regimen	Cost	QALY	ICER	$\lambda = £20,000$	Rank	$\lambda = £30,000$	Rank
12-month interval							
No surveillance	978	12.797		254,969	13	382,943	13
Mammography alone	1956	13.076	3513	259,559	1	390,317	1
Mammography + clinical	3384	13.084	173,840	258,295	7	389,135	5
MRI + clinical	6491	13.098	214,485	255,478	12	386,463	12
18-month interval							
No surveillance	978	12.797		254,969	13	382,943	13
Mammography alone	1703	13.052	2844	259,340	2	389,861	2
Mammography + clinical	2727	13.064	88,891	258,546	5	389,183	4
MRI + clinical	4958	13.085	105,565	256,738	10	387,586	6
24-month interval							
No surveillance	978	12.797		254,969	13	382,943	13
Mammography alone	1703	13.030	2295	258,906	3	389,210	3
Mammography + clinical	2727	13.044	45,211	258,161	8	388,604	8
MRI + clinical	4958	13.071	50,179	256,460	11	387,170	11
36-month interval							
No surveillance	978	12.797		254,969	13	382,943	13
Mammography alone	1468	13.011	2295	258,748	4	388,856	10
Mammography + clinical	2175	13.026	45,211	258,354	6	388,619	7
MRI + clinical	3716	13.057	50,179	257,427	9	387,999	9

TABLE 57 Sensitivity analysis for starting age of 40 years: IBTR

| Regimen | Cost (£) | QALY | ICER (£) | Net benefits (£) | | | |
				λ = £20,000	Rank	λ = £30,000	Rank
12-month interval							
No surveillance	4332	14.023		276,121	13	416,347	13
Mammography alone	11,383	16.013	3542	308,885	2	469,019	3
Mammography + clinical	12,859	16.093	18,630	308,994	1	469,920	2
MRI + clinical	15,970	16.237	21,569	308,767	3	471,136	1
18-month interval							
No surveillance	4332	14.023		276,121	13	416,347	13
Mammography alone	10,724	15.792	3613	305,109	7	463,026	7
Mammography + clinical	11,909	15.896	11,347	306,013	5	464,974	6
MRI + clinical	14,376	16.099	12,171	307,600	4	468,588	4
24-month interval							
No surveillance	4332	14.023		276,121	13	416,347	13
Mammography alone	10,176	15.598	3709	301,784	10	457,765	10
Mammography + clinical	11,239	15.717	8945	303,098	9	460,266	9
MRI + clinical	13,441	15.961	9033	305,772	6	465,378	5
36-month interval							
No surveillance	4332	14.023		276,121	13	416,347	13
Mammography alone	9693	15.431	3807	298,921	12	453,228	12
Mammography + clinical	10,692	15.556	7943	300,438	11	456,002	11
MRI + clinical	12,764	15.827	7663	303,775	8	462,045	8

Summary

In the base-case analysis the regimen with the highest net benefit and, therefore, most likely to be considered cost-effective was mammographic surveillance alone provided yearly. This result holds for women who had previously been treated for their primary cancer with either BCS or mastectomy or women who suffer IBTR.

As might be expected in a comparison of surveillance regimens, the results of the model are very sensitive to changes in the incidence of recurrent cancer. When the expected incidence is increased toward the maximum that could possibly be expected for any group of women mammography and clinical surveillance potentially becomes cost-effective when the surveillance interval is 24 months or longer. As the surveillance interval and incidence increase regimens that are more costly but more effective may also have incremental costs per QALY below typical threshold values. This suggests that there may be some scope for research into alternative technologies that could be used for surveillance.

The results of the analysis did not substantially alter for any of the other sensitivity analyses reported. The exception to this is when we changed several parameter values simultaneously. This was undertaken in an attempt to compare surveillance regimens for a hypothetical 40-year-old woman (who can be thought of as having a greater likelihood of developing

IBTR or MCBC) and a hypothetical 70-year-old woman (representing a lower likelihood of developing IBTR or MCBC). In the sensitivity analysis conducted for a 40-year-old woman, the following changes were made: the incidence of recurrent cancer was increased and the time it took for an undetected cancer to progress to risk profiles with a worse prognosis was reduced. Furthermore, it was assumed that should IBTR or MCBC be detected then it would be treated more aggressively (and at higher cost). For 40-year-old women facing these risks and costs, mammographic surveillance every 12 months had the highest net benefit, although it was only slightly greater than mammography and clinical follow-up every 12 months. These results suggest that a more intensive follow-up of women judged to be at high risk may be cost-effective. Conversely, for women at lower risk it may be more cost-effective for surveillance to be performed less often (every 2 or 3 years) with mammography alone or another similarly less intensive and costly test or tests.

Chapter 8

Discussion

Statement of overall aim and methods

Our aim was to examine the clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer in the UK in both primary and secondary care settings.

We addressed this by undertaking a survey of UK breast surgeons and radiologists to identify current practice and estimate resource consequences of the varying regimens. In addition, we undertook two discrete systematic reviews to determine the clinical effectiveness of differing surveillance mammography regimens carried out after treatment for primary breast cancer on patient health outcomes and the diagnostic accuracy of surveillance mammography in the detection of IBTR and MCBC. We undertook statistical analysis of individual patient data and economic modelling using the results of the systematic reviews and existing data sets, and focused searches for specific data analysis to determine the effectiveness and cost–utility of differing surveillance regimens.

We identified feasible management strategies for surveillance of women after treatment for breast cancer in a UK context, and have modelled the effectiveness and costs of these strategies. As is described later, we used these data to assess implications for clinical practice and to inform needs for future research.

Summary of main findings

The first two elements of research reported focused on describing and summarising current practice and current evidence with respect to mammographic surveillance after the treatment for primary breast cancer. Our survey of UK breast surgeons and radiologists described in *Chapter 3* suggests that although common patterns in surveillance mammography practice exist there is considerable variation in the combinations of start, frequency, duration and discharge from surveillance mammography.

The most common approach was to start surveillance mammography 12 months after initial surgery for the treatment of the primary breast cancer (87%), offer mammography annually (72%), organised through a symptomatic breast service (96%), discharging women (74%) after either 5 years (35%) or 10 years (55%). Over 55% stated that they discharged women to the NHSBSP for surveillance mammography to be carried out. Overall, 18% stated that they did not discharge patients from clinical follow-up but, of those who did, 65% discharged after 5 years with 22% discharging at 10 years after initial treatment.

Although our response rate was low (17%), which we discuss further below (see *Strengths and limitations*), we received responses from surgeons or radiologists working at 105 trusts across the UK. Our findings were concordant with previous surveys on this topic.[26,27] Therefore, we feel that our results are valid and informative, as they represent the views of the surgeons and radiologists involved in delivering breast cancer care and treatment from throughout the UK.

The plethora of different ways of conducting surveillance mammography in clinical practice means that there are potentially a large number of care pathways that are worthy of further consideration. It would not be possible to consider the merits of each of these options, especially when there are additional methods of follow-up that do not include mammography. Therefore, using the results of the survey and expert opinion from the project group a relatively small number of follow-up regimens was selected and defined. These differed in terms of the diagnostic technology used and the surveillance interval considered. It is possible, however, that potentially important pathways have been excluded from this list.

At the outset of this project, we felt that it would be important to evaluate the existing evidence regarding the effectiveness and cost-effectiveness of surveillance mammography, although we were unsure if the evidence base would be sufficient to guide any policy recommendations.

The systematic review we conducted to determine the effectiveness of differing surveillance mammography regimens after treatment for primary breast cancer in detecting IBTR and MCBC is described in *Chapter 4*. Our systematic review suggests that receipt of surveillance mammography offers a survival benefit compared with a surveillance regimen that does not include surveillance mammography. The surveillance regimens were complex and varied between studies (and only in broad terms could they be considered to fit within the different regimens of surveillance developed from the results of the survey). Furthermore, the influence of combinations of alternative surveillance regimens (e.g. clinical examination, ad hoc referral to the symptomatic service, etc.) remains unclear.

We adopted considerable and rigorous methods in an attempt to identify relevant studies. Despite this, only eight studies met our inclusion criteria, none of which was an RCT. We sought data from the included studies on eight outcomes, but few data on effectiveness, and none on cost-effectiveness, were identified. The limited and variable data that were available precluded any quantitative analysis, and the paucity of the underlying evidence base mirrors the findings of previous reviews.[4,29,43–47]

As we anticipated that the existing evidence base would not be sufficiently informative, we planned a formal systematic review of diagnostic performance and analyses of existing individual patient data held in potentially appropriate data sets and registries. We conducted this work not only because we felt the data sets to be important in their own right, but also to inform an economic evaluation.

We conducted a systematic review to determine the performance (diagnostic accuracy) of surveillance mammography, alone or in combination with other tests, in detecting IBTR and/or MCBC. The primary purpose of this review was to evaluate the test performance of surveillance mammography. Two studies reported sensitivity and specificity for surveillance mammography in detecting IBTR in patients undergoing routine surveillance; although we chose to describe results from the study by Boné and colleagues,[64] they should be treated individually owing to their highly selected patient population. The remaining study[66,67] reported a sensitivity of 67% and a specificity of 85% for surveillance mammography. The study authors included MRI as a comparator and reported 100% sensitivity and 93% specificity for MRI in this group of patients. Three studies[66,68,72] reported the median (and range) sensitivity and specificity of surveillance mammography for detecting IBTR in non-routine surveillance patients as 71% (50–83%) and 63% (57–75%), respectively. Two of these studies[68,72] included MRI and reported sensitivities of 93% and 100% and specificities of 88% and 96%, respectively. In detecting MCBC in patients undergoing routine surveillance, only one study[70] reported data for a single diagnostic test, MRI, with 91% sensitivity and 90% specificity.

Again, few data were available regarding MRI. Nevertheless, our findings suggest that MRI is the most accurate test for detecting IBTR and MCBC. Of the test combinations reported, surveillance mammography combined with breast ultrasound could be considered as the most accurate combination of tests for detecting MCBC.

We decided that it was inappropriate to use studies of population-screening mammography to calculate diagnostic test performance, as patients with breast cancer will have had treatment that may affect their breast density and the operation site can show marked changes due to scar tissue, with the adjacent parenchymal tissue changed as a result of postoperative radiotherapy. The sensitivity of mammography is reduced when a more sensitive test (MRI) is also used and this accounts for the difference in the literature with respect to screening mammography. Parameter estimates for MRI in the screening population were used in the economic evaluation in *Chapter 7* of this report, however, as it was felt that these would provide an indication of the relative value of a more costly but more effective test. Similarly, it was not possible to explore the effects of adjuvant treatments or any other subgroup effects that may have reduced breast density, and which theoretically would increase the sensitivity of surveillance mammography.

We have shown that IBTR has an adverse effect on survival. This is independent of the primary tumour and its characteristics, and in our analysis of BCS the HR was 2.13 (95% CI 1.78 to 2.56). This has been found in several previously published series.[20,77–80] Furthermore, the time from the treatment of the primary cancer to the event occurring is important, with those events that happen later having a survival advantage compared with those that occur earlier. This was also found in a combined analysis of five trials of women treated by BCS who had node-negative disease.[77]

We did not find that MCBC has an independent adverse effect on survival in either the BCS or mastectomy group. This is contrary to a large series of women with bilateral disease, who developed MCBC within 5 years of the primary tumour occurring and were under the age of 50 years. They were 3.9 times more likely to die than those who did not develop MCBC.[108] Our result may be due to there being too few deaths in our cohort with MCBC. We did find that older women are at reduced risk of MCBC and that women with larger tumours are at an increased risk of MCBC. It is known that women who have more advanced disease are at increased risk of developing contralateral disease. This needs to occur relatively early, as women with more advanced disease have poor survival. Therefore, it is likely that those women who develop MCBC later actually have a survival advantage from their primary disease. With respect to survival there was no evidence that women who develop MCBC have a different risk to those women who do not develop either IBTR or MCBC.

We have shown that there is a survival advantage if the IBTR or MCBC is detected at a smaller size compared with a larger size. The reference category was taken as < 10 mm in maximum diameter. Women with tumours of > 20 mm had an independent relative risk of death of 2.26 (95% CI 1.58 to 3.24). In those women for whom the data about size were missing (i.e. those women who did not have surgery) the risk of death is even greater at 3.19 (95% CI 2.24 to 4.53). While we have no information as to how these events were detected in clinical practice, the implication is that surveillance mammography may be of value. We know from the NHSBSP that 80% of cancers detected by 3-yearly mammography are < 20 mm in maximum diameter. This suggests that surveillance mammography could be used to reduce the size at which IBTR or MCBC cancers are detected. In our primary tumour cohorts the incidences of IBTR and MCBC are fairly constant over the first 10 years, although we did not follow this for a longer time period. This supports the fact that surveillance mammography should be continued for at least 10 years.

We used information derived from the prior analyses to inform the economic evaluation. The methods and results of this are reported in *Chapter 7*. The structure for the economic evaluation was informed by our survey, together with detailed discussions with clinical members of the research team. Rigorous and systematic attempts were then made to identify data relevant to the UK. These included the reviews and individual patient data analyses from existing data sets, and also included a series of focused reviews to identify other necessary data (e.g. on aspects of epidemiology/natural history of disease, health-state utilities, etc.). Despite these efforts, few data were available to inform many of the estimates used by the model and consequently the economic analysis should be considered as exploratory, and hence interpreted cautiously. Despite this, the results of the economic analysis suggest that the regimen with the highest net benefit, and therefore most likely to be considered cost-effective, was mammographic surveillance alone provided yearly. This result holds for women who were previously treated for their primary cancer with either BCS or mastectomy or for women who suffer an IBTR.

The results of the model were very sensitive to changes in the incidence of IBTR and MCBC. The maximum expected incidence modelled was 1.25% every 6 months. This exceeds the maximum that might be expected based on an interpretation of the Kaplan–Meier survival curves and the HRs reported in *Chapter 6* where there was moderate evidence of a statistically significant difference (i.e. the reported *p*-value was ≤ 5%). As the incidence of recurrent cancer increased to 0.9% every 6 months, a surveillance regimen of mammography and clinical surveillance potentially becomes cost-effective when the surveillance interval is 24 months or longer. This is because as incidence increases there is more scope for more costly regimens that have a better diagnostic performance to prove their worth. When the surveillance interval was increased to 36 months and the modelled incidence of IBTR and MCBC every 6 months was approaching 1%, a regimen of MRI and clinical follow-up also had an incremental cost per QALY below £30,000 (a typical threshold adopted by, for example, NICE). This suggests that there may be some scope for research into alternative technologies that could be used for surveillance for women at the highest risk of recurrence.

To test how robust the results were we explored the impact of changes in many of the other model parameters in a number of sensitivity analyses. The results of these analyses were not substantially different to the base-case results.

The exception to this was when we changed several parameter values simultaneously. This was carried out in an attempt to compare surveillance regimens for a hypothetical 40-year-old woman (where the model was changed so that a woman has a greater likelihood of developing IBTR and MCBC and has a worse prognosis) and a hypothetical 70-year-old woman (potentially representing a patient with less likelihood of developing IBTR and MCBC). In the sensitivity analysis conducted for a 40-year-old woman the following changes were made: the incidence of IBTR and MCBC cancer was increased and the time it took for an undetected cancer to progress to risk profiles with a worse prognosis was reduced. Furthermore, we assumed that should IBTR or MCBC be detected then it would be treated more aggressively (and at a higher cost).

For the scenario considering the cost-effectiveness of surveillance for a 40-year-old woman (a high-risk scenario) mammographic surveillance every 12 months had the highest net benefit, although it was only slightly greater than mammography combined with clinical follow-up every 12 months. These results suggest that a more intensive follow-up of women judged to be at high risk may be cost-effective. Conversely, for women at lower risk of IBTR or MCBC (the scenario modelled was for a 70-year-old woman) it may be more cost-effective for surveillance to be performed less often (every 2 or 3 years) with mammography alone or another similarly less intensive and less costly test or combination of tests.

Taken together, the results of the economic analysis would suggest that were the NHS to adopt a single policy covering all women after treatment for a primary breast cancer then a policy of mammographic surveillance alone at 12, 18 or 24 months might be the best policy. If the base-case analysis underestimated the risk of IBTR or MCBC then a more intensive regimen, for example mammography and clinical follow-up, might be more efficient, although because of the trade-off between cost and diagnostic performance the surveillance interval might increase to 24–36 months. Were the NHS to consider targeting intensive surveillance for those deemed at higher risk of recurrence then it is possible that more intensive methods of surveillance would be considered worthwhile given the conventional threshold for society's willingness to pay for a QALY. For women deemed at lower risk of recurrence a less intensive regimen may be the most cost-effective. This raises questions about the feasibility of providing different patterns of surveillance according to perceived risk of recurrence. It also raises questions about the ethics of treating women who have been treated for a primary breast cancer differently, based not just upon characteristics of their primary cancer, but also other demographic characteristics such as age.

Strengths and limitations

Our work focused on the question posed by the HTA programme: what is the clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer? Mammography is the primary follow-up examination conducted in the UK at the present time in clinical practice. For this reason, our survey and systematic reviews concentrated on surveillance mammography, although other tests were considered when reported with mammography results in this particular patient population. Overall, we believe the main strengths of this project are the rigorous, systematic, explicit and comprehensive methods used. We have identified that there is limited evidence available to answer our research question and, as such, this is the main limitation of our findings.

Identifying feasible management strategies for surveillance and follow-up of women after treatment for breast cancer (Chapter 3)

Our survey findings reflect the different guidance given by the various professional organisations with an interest and expertise in surveillance following treatment for breast cancer in combination with 'local circumstances' and protocols of the respondents (see *Table 10*). Our findings are generally consistent with those of recent surveys addressing similar questions. Donnelly and colleagues' survey[26] of 256 specialists registered to Cancer Trials Units suggested that the majority (84%) adhered to locally developed protocols and that mammography at annual intervals was the most common surveillance interval for both invasive and non-invasive primary breast cancer. Respondents favoured a risk-adjusted protocol and their preferred median clinical follow-up time overall was 5 years. Maxwell and colleagues' survey[27] of breast-screening units taking part in the Sloane project concluded that there was wide variation in follow-up practice after surgery (breast conservation or mastectomy) for non-invasive breast cancer, the most common frequency and duration of clinical follow-up being annually for the first 5 years after treatment, and surveillance mammography being annually for the first 10 years in patients undergoing breast conservation, and annually or 2-yearly in patients who had undergone a mastectomy, also for 10 years.

The final response rate to our survey was low compared with other recent similar surveys.[26,27] Cook and colleagues[109] recently reported in a review of response rates of surveys of health-care professionals that response rates are low and probably declining [average response rate in doctors was 57.5% (95% CI 55.2% to 59.8%), but this is significantly lower than the estimate for the

prior 10-year period]. Rates are lower without a reminder and with larger surveys. Our survey was a 'cold-calling' mass e-mailing with no personal reminders to complete the survey, whereas the sample taking part in these previous surveys was a selected population with an interest in clinical trials or taking part in national audit. Our response rate also highlights the disadvantages of undertaking an anonymous survey, as it is probable that our low response rate would have been improved if we could have used personal reminders to non-responders. Our low response rate may mean our results are not representative of the population of health-care professionals organising, providing and overseeing the follow-up care of women after surgery for primary breast cancer. However, taken together with data from Donnelly and colleagues[26] and Maxwell and colleagues,[27] it has provided an insight into the more common patterns of surveillance mammography practice and the feasible strategies for follow-up.

Systematic review of effectiveness of surveillance mammography after treatment for primary cancer (Chapter 4)

The methods used for conducting the review of the clinical effectiveness and cost-effectiveness of surveillance mammography were systematic, explicit and comprehensive. We believe that our inclusion criteria were both clinically relevant and scientifically rigorous. The main limitation of the review relates to the limitations of the underlying evidence base. Few published studies met the inclusion criteria, none of which was an RCT. Few data were available and what data were available were potentially biased. Owing to limited data and variability across studies we felt it unwise to perform a meta-analysis, thus a narrative synthesis of evidence was presented. The included studies are likely to be prone to both lead and length time bias. There was no comparison of varying surveillance mammography regimens. An RCT study design with survival as the end point would take these biases into account as the random allocation of participants to intervention groups minimises the impact of bias due to confounding variables. Such a study would be possible, as equipoise exists as to the ideal interval between surveillance mammograms.

It is possible that there are unpublished reports that may have otherwise met our inclusion criteria. The clinical members of the research team did not suggest any potentially relevant work that we could have included and, at the time of writing this report, we are unaware of any unpublished studies meeting our inclusion criteria.

Health-related quality of life was included as a review outcome and we were not restrictive in the measures that we considered. Some of the potential methods could have captured the effects on the psychological health of the woman. Nevertheless, we did not explicitly consider psychological factors as outcomes. This may be of greater concern in the NHSBSP, in which women who are 'well' are invited for mammography, because psychological harm or anxiety due to the examination or a suspicious test result or a false reassurance could have greater adverse impact. It is, however, worth noting that none of the included studies reported quality-of-life data and it is unclear if any would have provided data regarding psychological outcomes.

Systematic review of the test performance of mammography and comparator tests in detecting IBTR/MCBC (Chapter 5)

We believe that the methods adopted for this review are scientifically rigorous and compatible with current guidance in this area. Very few studies met our review inclusion criteria. The included studies were restricted to those published in the English language. This potentially limits the evidence base available, although non-English-language studies were less likely to be relevant to UK practice. As with the review of clinical effectiveness and cost-effectiveness we deliberately chose broad participant inclusion criteria. We based our rationale for this decision on our preliminary knowledge of the limited evidence base available. Narrowing our inclusion criteria would further limit the amount of available data. Although broadening our inclusion criteria carried the risk of finding variation between studies we believe that the limited data presented

have greater generalisability to the whole spectrum of women who would be offered surveillance in practice. Of the studies included here, few evaluated the performance of the considered tests for similar purposes. Furthermore, even where data were available it was not clinically appropriate to combine them. For example, because of anatomical differences between a 'treated' and an 'untreated' breast (due to the effects of treatments) it was not appropriate to combine data on test performance for the detection of IBTR and MCBC. Similarly, it was inappropriate to combine data from routine and non-routine surveillance patients, as the test operator is primed to evaluate a suspicious finding in the non-routine surveillance patient. It is unclear what effect this has on test accuracy but it is likely to focus their attention on a particular area of the breast and may conceivably increase the sensitivity of the diagnostic test. Furthermore, no data were reported by the studies included on other test performance factors, such as adverse effects or acceptability of the tests.

Systematic reviews of diagnostic accuracy are highly complex and methodology in this area continues to evolve. One of the problems with a diagnostic review in this area is that there is not an established reference standard for ascertaining the true- and false-negative results of a surveillance test for IBTR or MCBC breast cancer. One potential solution is that true- and false-negatives are ascertained by a negative result or a positive test result at subsequent testing after a period of follow-up has elapsed. While this represents a pragmatic reference standard for verifying negative test results it introduces the possibility of an interval cancer occurring during the time period between tests.

Disease progression bias refers to instances where there is a time delay between an index test result and administration of the reference standard test, thus allowing the possibility of a misclassified reference standard test result. In breast cancer, uncertainty might exist as to whether a false-negative index test truly represents a cancer missed at the time of administering the index test, or whether a positive test result on subsequent testing represents a cancer that has occurred in the time interval after administration of the index test and before verification via the subsequent surveillance test. The possibility of this bias can be minimised through short time intervals between test administrations, although it cannot be completely eliminated. All studies in this review were considered to have adequate time intervals for verifying negative results for all tests. Similarly, we defined a time interval of no longer than 3 months between a positive test result and confirmation by reference standard assessment by fine-needle aspiration cytology or tissue biopsy, and no longer than 6 months for histopathological assessment by biopsy. The time period between a positive test result and reference standard confirmation was unclear in all but one study.[71]

Results for the index and comparator tests evaluated in this review were ascertained by subjective operator interpretation, either by visual inspection of an image of the breast (surveillance mammography, ultrasound and MRI) or by clinical examination of the breast. We do not have available data on the level of operator expertise or intra/inter-rater reliability for the included studies. It is therefore unclear whether these factors had any influence on reported test accuracy within, and between, studies and therefore whether any potential test operator bias exists.

Analysis of breast cancer data set (Chapter 6)

The strength of this analysis is that it is based on a large consecutive cohort of women diagnosed with breast cancer in the UK and treated within the NHS. The data have been collected prospectively and without selection bias. There were a large number of IBTR and MCBC events. The results of this analysis are generalisable to the UK as the WMCIU collects information from a large geographical area with a population of over 5.3 million. We used the time period from 1997 onwards to ensure consistency in data coding. As discussed earlier, this time period reflects the current management and follow-up of breast cancer patients and was after the introduction

of the screening programme. Some previous analyses, although having the advantage of longer follow-up, cover time periods where cancer diagnosis and treatment were different.[108] Our large data set allowed us to model the effects of IBTR and MCBC, and the time when they occurred, on survival and to examine whether these were independent risk factors.

The limitations of this analysis are that the data set did not contain information on surveillance mammography required to assess the effectiveness of such a regimen on survival after breast cancer treatment (i.e. frequency and duration of surveillance regimen). We used an NHS cancer data set, which was reflective of routine data collection within the NHS, although not as intensively populated or meticulously recorded as a trial data set. It was only possible to have a maximum of 10 years of follow-up because we wanted to ensure that our results were relevant to current practice. The shorter median follow-up time will possibly have the effect of underestimating the long-term adverse effect of second cancers. The data set did not contain information on whether the IBTR/MCBC were detected by mammography or clinical examination or from the patient's symptoms but we could not expect this as this is not routinely recorded by cancer registries. Women who did not have surgery for their primary breast tumour were not included in our analysis. This was because curative intent was unlikely when they were treated. Logically, it would be inappropriate to offer them surveillance mammography in the same way as women following curative treatments. A small number of older women are treated with endocrine therapy and possible radiotherapy if the tumour progresses while on hormone therapy. In addition, those who are ER negative and unfit for surgery may have radiotherapy and are monitored by mammography but this was not felt to equate with surveillance mammography.

There were perhaps fewer IBTR and MCBC events than expected compared with many published studies. For example, the recent Guy's data set reported a cumulative 10-year combined IBTR/MCBC risk of 0.11 (95% CI 0.09 to 0.14) in patients undergoing BCS, whereas this was 0.071 (95% CI 0.065 to 0.077) in the WMCIU data set.[110] This is most probably due to the relatively short follow-up time compared with the Guy's data set (median 9 years compared with median 5 years). The WMCIU data set also only includes those patients who have had pathological confirmation of IBTR or MCBC, and this partly accounts for the apparent underascertainment of events in the WMCIU data set. The Guy's data set was meticulously collected and the IBTR or MCBC events continued to be collected even after distant metastases were found. In some clinical practices, once distant metastases are found, breast cancer follow-up, with respect to detection of IBTR and MCBC, is not consistently undertaken, thus such events may not be recorded. We did not incorporate information about distant metastases and so could not censor at this time point. It is possible that this accounts for the apparent lack of worse prognosis for those women who develop an MCBC compared with women who do not develop further breast cancer.

It is important to recognise that the second tumour cohort data set that we used to inform the risk of death from IBTR or MCBC was created by taking all events from 1990 onwards from women who had been treated surgically for primary breast cancer. This was performed in order to have a sufficiently long follow-up period to calculate long-term survival in a large sample. Although they contain related information, the data sets should be treated independently and therefore information not extrapolated from one to another.

*Economic evaluation (*Chapter 7*)*

The main strength of the economic evaluation is that it has attempted to use rigorous and systematic methods to obtain parameter inputs into the economic evaluation. These were then assembled in the economic model whose structure was informed by both detailed discussions with the clinical members of our research team and the results of the survey of current and desired practice, commissioned as part of this study. One of the most important challenges faced when conducting the economic evaluation was the limited evidence base available. This

constrained the model in a number of key ways. First, there were insufficient data available to model all the potential strategies that we considered relevant, and, second, few data were available on many model parameters. Furthermore, what data were available were not ideally suited to the question being addressed. For example, for health-state utilities few data relevant to a UK decision-making context were identified. In response to this, we adapted our plans to focus on three basic patterns of surveillance, the cost-effectiveness of which was explored in extensive sensitivity analyses. The object of these sensitivity analyses was not necessarily to provide definitive conclusions about the best regimen for the UK to adopt but rather to identify 'best bets' that would be worthy of further consideration. Our economic evaluation did not model all the commonly used surveillance regimens in the UK. This, in part, was due to limitations in existing evidence, but also because there were so many variants.

A further limitation relates to the way the available data were structured in the economic analysis. The model structure contains a number of simplifying assumptions. First, IBTR and MCBC are treated identically and it is assumed that they are of the lowest level of severity at the point where it is technically possible to detect them. Severity of disease has also been defined in an arbitrary manner (by grouping cancers according to the expected 10-year survival). This was driven, in part, by a desire to keep this element of the model manageable. However, it may mean that relatively subtle differences between strategies might be missed.

The economic evaluation took the UK NHS as its perspective. This meant that only costs incurred by the NHS were included, and benefits were measured in terms of the effects on health (measured in QALYs) that were consequent on increased survival caused by earlier detection. This perspective is the one recommended by NICE,[100] for instance, but it means that other potentially important costs and benefits are excluded. With respect to costs it might be expected that the women's costs of accessing surveillance services would increase as the frequency of surveillance increases. However, earlier detection and successful treatment would reduce time away from usual activities following treatment and those caused by ill health attributed to more advanced disease. The net effect of these aspects is uncertain.

Similarly, this project did not consider psychological implications for women and their families. Quality-of-life measures used as the basis of QALYs can capture some aspects of the effects on anxiety and mental health. However, the model only considered those effects relating to health effects from treatment/non-treatment of the cancer. It did not consider the whole patient experience of undergoing surveillance. We sought opinion from the patient representative member of our Advisory Group regarding our results. Variation in the manner in which surveillance is organised can be a source of anxiety to women due to concerns that differences in frequency and duration of follow-up have implications for risk of recurrence and survival. A woman could, for example, assume that 10 compared with 5 years of follow-up implies that she is at a heightened personal risk of developing IBTR or MCBC, rather than being an association with eligible screening age or local practice. Similarly, a patient undergoing mammography every 3 years compared with one having annual mammography may either feel reassured that she has less risk of developing further cancer or feel anxiety that any further cancer will go undetected for a greater length of time. With respect to the model, these aspects could be further explored using preference elicitation techniques that go beyond the QALY framework. In more practical terms, this concern highlights the potential need to ensure that patients with breast cancer have a greater understanding of how and why their follow-up regimen has been 'personalised' to match their personal breast cancer type and its risk factors. Greater standardisation of practice in timing of implementing and discharging surveillance regimens would also provide reassurance that patients throughout the UK are all receiving the same standard of care.

Chapter 9

Conclusions

Summary of findings

The most common mammographic surveillance regimen identified by our survey was annual mammography commencing 12 months after surgical treatment of the primary breast cancer. There was considerable variation in the combinations of start, frequency, duration and discharge from different surveillance regimens, however. Prior to our work, there was little existing evidence on the effectiveness of surveillance mammography and follow-up after treatment for primary breast cancer. Our systematic review of clinical effectiveness suggests that surveillance mammography offers a survival benefit compared with a surveillance regimen that does not include surveillance mammography. However, the effects of combinations of alternative surveillance regimens (e.g. clinical examination, referral to secondary care between planned surveillance if the patient has symptoms, etc.) remain unclear. Few data were identified regarding the diagnostic performance. The few data we found suggest that mammography is associated with a high sensitivity and specificity but MRI is the most accurate test for detecting IBTR and MCBC. The results from the systematic reviews should be interpreted with caution due to the limited evidence base from which they are derived (effectiveness review, eight studies; test performance review, nine studies).

No existing data set was identified that was ideally suited to answering our research questions. Our analysis of the WMCIU data set confirmed the previously known risk factors for mortality from breast cancer. It also demonstrated that IBTR is an independent predictor of survival. For women experiencing IBTR size is important, with those women with tumours > 20 mm in size being at a significantly greater risk of death than those with IBTR of < 10 mm. There was no evidence that MCBC is an independent predictor of survival; however, in women who do experience MCBC the size of the tumour is important. Women with tumours > 20 mm in size are at a significantly greater risk of death than those with MCBC tumours of < 10mm. Given the limited evidence base the results of the economic evaluation should be considered as exploratory. If it were decided that the NHS should adopt a single surveillance regimen for all women then the economic evaluation suggests that the regimen most likely to be considered cost-effective when the cost per QALY threshold was either £20,000 or £30,000 would be mammographic surveillance alone, provided every 12–24 months. The results of the economic model were sensitive to incidence and other factors, for example age, tumour characteristics, etc., that might define groups of women with greater or lesser likelihoods of developing a IBTR or MCBC. These results suggest that a more intensive follow-up of women judged to be at greater likelihood might be worthwhile. Conversely, for women with less likelihood it may be more cost-effective for surveillance to be performed less often (every 2 or 3 years) with mammography alone.

Implications for the NHS and patients

- Results suggest that surveillance, when combined with effective treatment of the cancers detected, is likely to improve survival.
- The evidence base on which to recommend any change in current practice is relatively weak.

- The current evidence base suggests that should the NHS choose to standardise surveillance for all women then a regimen of mammography alone every 12–24 months appears to have the highest net benefits when society's willingness to pay for a QALY is £20,000 or £30,000.
- Rather than offering the same regimen to all patients, careful consideration should be given to stratification of patients to ensure maximum benefit to ensure optimal use of resources. How best to deliver a varying surveillance regimen would be challenging, and consideration is also needed about how such a service could be best organised.
- The current evidence base suggests that should the NHS choose to tailor surveillance for those women with a greater likelihood of developing IBTR or MCBC then more comprehensive (e.g. mammography and clinical follow-up) and more frequent surveillance (every 12 months) would be associated with the greatest net benefit.
- The current evidence base suggests that should the NHS choose to tailor surveillance for those women least likely to develop IBTR or MCBC then only less frequent mammographic surveillance (e.g. every 36 months) would be associated with the greatest net benefit.
- Variation in surveillance practice (e.g. frequency and duration of follow-up regimen) can be a source of anxiety to women. This implies that efforts to improve the patient's understanding of how they will be followed up are important. Should the NHS choose to tailor surveillance then there would need to be the provision of information and reassurance about how the follow-up regimen has been tailored to match the type of breast cancer they have had and their risk factors for developing IBTR or MCBC.
- Although evidence is limited about how best to standardise practice greater standardisation of an agreed surveillance regimen would provide reassurance that patients throughout the UK are receiving the same standard of care.

Suggested research priorities

Further evidence is required to make a robust and informed judgement on the effectiveness of mammographic surveillance and follow-up. From a scoping search conducted on 25 August 2010, 14 months after conducting the search for the main effectiveness systematic review, we identified 192 potential titles and abstracts. Of these, we found no RCT studies directly addressing our research question. We found one RCT for which primary outcomes considered psychological morbidity for point of need compared with 6-monthly clinic surveillance. Only the secondary outcomes of this RCT, recurrences and method of detection, are relevant for this report. We found six non-RCT studies, two of which are referenced in the introductory section of this report,[5,48] providing indirectly relevant evidence. We found no new HTA report or ongoing RCTs. The evidence trajectory for the clinical and cost-effectiveness of surveillance mammography therefore appears to be slow moving. Research is suggested in the following areas:

- The data sets that exist at the moment are an excellent resource for researchers and considerable further analysis, addressing both clinically and economically important questions, could be undertaken using the data they contain. For example, further work could focus on extending our analyses by incorporating the influence of distant metastases on survival. Where appropriate such analyses should be incorporated into an economic evaluation model.
- With respect to the research question posed within this report the utility of the data sets could be improved. The optimal data set would record details of mode of detection for IBTR or MCBC; the frequency of the clinical and mammographic surveillance regimen, and how this varies over time; and whether a woman's IBTR or MCBC was detected during routine surveillance or as a result of it causing symptoms for the patient. Some of this information is well collected currently and additional information might reasonably be captured in a thorough audit. It is important to record accurate and timely information on

grade, size, tumour type, ER status and lymph node status of both the primary tumour and subsequent IBTR or MCBC tumour; details of the primary treatment given (i.e. type and extent of surgery, excision margins, radiotherapy, hormone therapy, chemotherapy and other treatments); details of IBTR or MCBC treatment; when and where distant metastases occurred; and cause of death. Once available such data should be incorporated into refined statistical and economic analyses addressing the research question posed within this report.

- The paucity of data on the diagnostic performance of tests in the group of women of interest needs to be addressed. There is a need for high-quality, direct head-to-head studies comparing the diagnostic accuracy of tests used in the surveillance population. Such studies are likely to be lower cost than a definitive RCT and provide data sooner. Such data should then be incorporated into an economic evaluation model.

- The economic evaluation suggested that there were circumstances where the use of tests with a better diagnostic performance but higher cost might be potentially cost-effective. Further primary work should also consider whether the use of existing technologies, such as MRI, which may have better performance, could be worthwhile for patients at high risk of IBTR or MCBC. An economic analysis should form part of such work.

- It would be useful to compare within an economic evaluation mixed clinical follow-up in lower cost settings combined with surveillance mammography in the long term. It would also be important to consider psychological factors associated with differing types, settings and frequency of surveillance regimens using a major health psychology theory so that the economic modelling could focus down on regimens that, based on the psychological analyses, look most promising.

- A definitive RCT would be ideal and, although costly, could focus on those women at higher risk of IBTR or MCBC. The interventions considered might include mammography and MRI, for those at the highest risk, or surveillance mammography of 1 year versus a longer time interval, for example 3 years. Such a trial might also compare more sophisticated surveillance regimens that vary not only in terms of the frequency of mammography, but also in terms of the frequency and setting of clinical follow-up.

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Contributions of authors

Fiona Gilbert led the drafting of the Background chapter. Clare Robertson wrote the initial draft with advice from Steve Heys.

Luke Vale and Laura Ternent led the drafting of *Chapter 2*.

Ruth Thomas led the drafting of *Chapter 3*, identifying feasible regimens, with Luke Vale.

Clare Robertson developed the protocol and undertook the survey described in *Chapter 3*, working closely with Ruth Thomas.

Clare Robertson led the systematic reviews with advice from Graham Mowatt. She developed the protocols for the systematic reviews working closely with Ruth Thomas and led the drafting of the systematic review chapters (*Chapters 4* and *5*).

The systematic review team of Charles Boachie, Graeme MacLennan, Clare Robertson, Ruth Thomas and Shihua Zhu undertook the effectiveness review (*Chapter 4*).

The systematic review team for *Chapter 5* was Charles Boachie, Fiona Gilbert, Graeme MacLennan, Jennifer Hislop, Clare Robertson, Senthil Kumar Arcot Ragupathy, Ruth Thomas and Shihua Zhu.

Graeme MacLennan led the drafting of *Chapter 6*, the analysis of the existing data sets, with advice from Steve Heys and Fiona Gilbert. Graeme MacLennan developed the protocol and led

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Appendix 1

Membership and individual area of expertise of the project Advisory Group

Aberdeen working group

Charles Boachie (Statistician)

Cynthia Fraser (Information Specialist)

Fiona Gilbert (Roland Sutton Chair of Radiology/Chief Investigator)

Steve Heys (Professor of Surgical Oncology, Chair of Applied Medicine)

Graeme MacLennan (Senior Statistician)

Graham Mowatt (Senior Research Fellow – Lead Systematic Review Team)

Clare Robertson (Research Fellow – Systematic Reviewer)

Laura Ternent (Research Fellow – Health Economics)

Ruth Thomas (Senior Research Fellow – Project Manager)

Luke Vale (Senior Research Fellow – Health Economics)

HTA grant co-applicants

Mike Dixon (Consultant Breast Surgeon)

Sarah Pinder (Professor of Breast Pathology)

Robin Wilson (Consultant Radiologist)

Expert panel

Val Bain (Breast Care Nurse)

Peter Donnelly (Consultant Breast Surgeon)

Wilma Jack (Senior Clinical Research Fellow, Edinburgh data set)

Gill Kerr (Statistician, Edinburgh data set)

Gill Lawrence (Director, WCMIU)

Anthony Maxwell (Consultant Radiologist)

Jean McGregor (Patient Representative, Breast Cancer Care Support Volunteer)

Peter Murchie (GP, Clinical Senior Lecturer)

Appendix 2

Questionnaire content: a survey of UK surveillance mammography practice after treatment for primary breast cancer

UNIVERSITY OF ABERDEEN
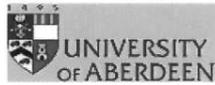
Department of Radiology

Survey of Surveillance Mammography Practice after treatment of Primary Breast Cancer

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This questionnaire is about your current and ideal surveillance mammography practice for women who have had breast conserving surgery or mastectomy for primary breast cancer. This survey should take no longer than 5-10 minutes to complete.

| Page 1 | Page 2 | Page 3 | Page 4 |

Section A : Background

1. What is your speciality   [Please select... ▼]   If other, please describe [   ]

2. Please name your NHS Trust (please write in full instead of abbreviating)   [   ]

3. How many women with newly diagnosed breast cancer does your unit manage annually (include both symptomatically and screen-detected)   [Please select... ▼]

4. How soon after completing surgery for primary breast cancer do you initiate surveillance mammography? (answer in months)   [   ] months

Section B : Your Standard Surveillance Mammography Practice

For women who have had breast conserving surgery

5. Please describe your standard surveillance mammography for women who have had breast conserving surgery

I arrange surveillance mammography   [Annually ▼]   If other, please describe [   ]

[Next >>]

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7e. ☐ Age ... for which ages do you vary your standard surveillance mammography practice

    e.g. under 30 years

How soon after completing breast conserving surgery for primary breast cancer do you initiate surveillance mammography?

How often do you arrange surveillance mammography?

Please select... ▼ | If other, please describe

7f. ☐ Absence of radiotherapy

How soon after completing breast conserving surgery for primary breast cancer do you initiate surveillance mammography?

How often do you arrange surveillance mammography?

Please select... ▼ | If other, please describe

7g. ☐ Combination of criteria above ...

    e.g. women under 30 who has lymphovascular invasion

Please describe which criteria you combine

How soon after completing breast conserving surgery for primary breast cancer do you initiate surveillance mammography?

How often do you arrange surveillance mammography?

Please select... ▼ | If other, please describe

7h. ☐ Other ... Other criteria not listed above

How soon after completing breast conserving surgery for primary breast cancer do you initiate surveillance mammography?

How often do you arrange surveillance mammography?

| Page 1 | Page 2 | **Page 3** | Page 4 | | Confirm screen |

For women who have had mastectomy

8.　Please describe your surveillance mammography practice for the contralateral breast for women who have had mastectomy

8a.　I initiate surveillance mammography ☐ after mastectomy for primary breast cancer

8b.　I arrange surveillance mammography [Please select... ▾] If other, please describe ☐

9.　Do you ever vary your standard surveillance mammography practice for the contralateral breast for women who have had mastectomy? [Please select... ▾]

10.　Please describe the critieria you use for varying your standard surveillance mammography for the contralateral breast for women who have had mastectomy ☐

How soon after completing breast conserving surgery for primary breast cancer do you initiate surveillance mammography? ☐

How often do you arrange surveillance mammography? [Please select... ▾] If other, please describe ☐

| Page 1 | Page 2 | Page 3 | **Page 4** | | Confirm screen |

Section C: Surveillance Mammography Scheduling and Discharge

11. Through which service is your surveillance mammography scheduled?

Please select...

12. If eligible do you discharge women into the screening programme for surveillance mammography?

Please select ..

If yes, at what age do you discharge

13. Do you discharge women from clinical follow up?

Please select...

If yes, please indicate when

years post surgery for primary breast cancer

13b. Do you discharge women from surveillance mammography follow up?

Please select...

If yes, please indicate when

years post surgery for primary breast cancer

14. Are there any exceptions to your normal surveillance mammography practice (e.g. patient participating in a clinical trial)?

Please select...

If yes, can you specify what this would involve?

15. Does your current surveillance mammography practice differ from how you would ideally like to arrange surveillance mammography?

Please select...

16. Can you please indicate how often you would ideally like to arrange surveillance mammography?

16a. How often would you ideally arrange surveillance mammography for women who have had breast conserving surgery?

Please select...

If other, please describe

16b. How often would you ideally arrange surveillance mammography for women who have had mastectomy?

Please select...

If other, please describe

17. If your current surveillance mammography practice differs from your ideal surveillance mammography practice what factor influence this difference?

18.

Please use this space to provide any comments

<< Previous   Next >>

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Appendix 3

E-mail invitation to participate in a survey of UK surveillance mammography practice after treatment for primary breast cancer

From: hsru.notification.service@abdn.ac.uk

Sent:

To:

Subject: Survey of UK Surveillance Mammography practice after treatment for primary breast cancer

Survey of UK Surveillance Mammography practice after treatment for primary breast cancer

We are inviting you to complete an online questionnaire about your current surveillance mammography practice (please see web link below). We are surveying members of the Association of Breast Surgery at BASO and the Royal College of Radiologists Breast Group. The survey is part of a National Institute for Health Research, Health Technology Assessment programme commissioned study (HTA Project 07/47/01 – to determine the clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment of primary breast cancer in the UK). The study is being conducted by a multidisciplinary research team led by Professor Fiona Gilbert (Roland Sutton Chair of Radiology) at the University of Aberdeen.

The questionnaire should take no longer than 5–10 mins to complete. Your valuable participation will contribute towards identifying the clinical and cost-effectiveness of differing surveillance mammography regimens, and help to identify future research priorities in this area. We would be very grateful if you would consider helping us with our important research.

The questionnaire is strictly confidential and anonymous. In order to ensure anonymity, please note that you will not be able to save your responses and return to the survey at a later stage. Please review your responses before clicking 'submit' to send your completed survey. You will not be able to return to your responses after submitting the survey.

Please click on the web link below to begin the questionnaire. Thank you very much for giving your time to help us with our research.

https://viis.abdn.ac.uk/HSRU/htamammography/default.aspx?uid=52b54a34-12d1-41f8-86d8-b60786762426

If you have any queries or comments about the questionnaire or the research study, please contact:

Clare Robertson
Research Fellow
Health Services Research Unit
University of Aberdeen
3rd Floor, Health Sciences Building
Aberdeen AB25 2ZD

Appendix 4

Reminder e-mail invitation to participate in a survey of UK surveillance mammography practice after treatment for primary breast cancer

From: hsru.notification.service@abdn.ac.uk

Sent:

To:

Subject: REMINDER: Survey of UK Surveillance Mammography practice after treatment for primary breast cancer

REMINDER: Survey of UK Surveillance Mammography practice after treatment for primary breast cancer

You may have already received an e-mail inviting you to participate in this survey. If you have already completed and returned the questionnaire, please accept our thanks and delete this e-mail as no further involvement is required. If you have not completed the questionnaire please take the time to consider helping us with this important research.

We are inviting you to complete an online questionnaire about your current surveillance mammography practice (please see web link below). We are surveying members of the Association of Breast Surgery at BASO and the Royal College of Radiologists Breast Group. The survey is part of a National Institute for Health Research, Health Technology Assessment programme commissioned study (HTA Project 07/47/01 – to determine the clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment of primary breast cancer in the UK). The study is being conducted by a multidisciplinary research team led by Professor Fiona Gilbert (Roland Sutton Chair of Radiology) at the University of Aberdeen.

The questionnaire should take no longer than 5–10 mins to complete. Your valuable participation will contribute towards identifying the clinical and cost-effectiveness of differing surveillance mammography regimens, and help to identify future research priorities in this area. We would be very grateful if you would consider helping us with our important research.

The questionnaire is strictly confidential and anonymous. In order to ensure anonymity, please note that you will not be able to save your responses and return to the survey at a later stage. Please review your responses before clicking 'submit' to send your completed survey. You will not be able to return to your responses after submitting the survey.

Please click on the web link below to begin the questionnaire. Thank you very much for giving your time to help us with our research.

https://viis.abdn.ac.uk/HSRU/htamammography/default.aspx?uid=52b54a34-12d1-41f8-86d8-b60786762426&Reminder=true

If you have any queries or comments about the questionnaire or the research study, please contact:

Clare Robertson
Research Fellow
Health Services Research Unit
University of Aberdeen
3rd Floor, Health Sciences Building
Aberdeen AB25 2ZD

Appendix 5

Number and percentage of respondents completing questions in the survey of UK surveillance mammography practice after treatment for primary breast cancer

	Question	$n=183$	Percentage of n
1	What is your specialty?	183	100
2	Please name your NHS trust	182	99
3	How many women with newly diagnosed breast cancer does your unit manage annually (include both symptomatically and screen detected)?	183	100
4	How soon after completing surgery for primary breast cancer do you initiate surveillance mammography? (answer in months)	181	99
5	Please describe your standard surveillance mammography for women who have had BCS:		
	I arrange surveillance mammography (give frequency)	182	99
6	Do you ever vary your standard surveillance mammography practice for women who have had BCS? (filter question)	180	98
7	If yes please tick all below that apply:		
7a	In situ cancers (DCIS, LCIS):	14	8
	For which in situ tumours do you vary your standard surveillance mammography practice?	11	6
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	14	8
	How often do you arrange surveillance mammography?	13	7
7b	Primary tumour size:	5	3
	For tumours above what size do you vary your standard follow up (in cm)	4	2
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	4	2
	How often do you arrange surveillance mammography?	4	2
7c	Primary tumour grade:	4	2
	For which grades(s) do you vary your standard surveillance mammography practice?	4	2
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	4	2
	How often do you arrange surveillance mammography?	4	2
7d	Lymphovascular invasion:	4	2
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	4	2
	How often do you arrange surveillance mammography?	3	2
7e	Age:	9	5
	For which ages do you vary your standard surveillance mammography practice?	9	5
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	9	5
	How often do you arrange surveillance mammography?	9	5
7f	Absence of radiotherapy:	3	2
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	3	2
	How often do you arrange surveillance mammography?	2	1

	Question	$n=183$	Percentage of n
7g	Combination of criteria above:	2	1
	Please describe which criteria you combine	1	1
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	1	1
	How often do you arrange surveillance mammography?	1	1
7h	Other:	10	5
	Other criteria not listed above	8	4
	How soon after completing BCS for primary breast cancer do you initiate surveillance mammography?	6	3
	How often do you arrange surveillance mammography?	7	4
8	Please describe your surveillance mammography practice for the contralateral breast for women who have had mastectomy		
8a	I initiate surveillance mammography x months after mastectomy for primary breast cancer	159	87
8b	I arrange surveillance mammography (give frequency)	181	99
9	Do you ever vary your standard surveillance mammography practice for the contralateral breast for women who have had mastectomy? (filter question)	180	98
10	Please describe the criteria you use for varying your standard surveillance mammography for the contralateral breast for women who have had mastectomy	20	11
	How soon after completing mastectomy surgery for primary breast cancer do you initiate surveillance mammography?	23	13
	How often do you arrange surveillance mammography?	24	13
11	Through which service is your surveillance mammography scheduled?	182	99
12	If eligible do you discharge women into the screening programme for surveillance mammography?	179	98
	If yes, at what age?	39	21
13	Do you discharge women from clinical follow up?	180	98
	If yes, please indicate when	130	88
13b	Do you discharge women from surveillance mammography follow-up?	182	99
	If yes, please indicate when	121	89
14	Are there any exceptions to your normal surveillance mammography practice (e.g. patient participating in a clinical trial)?	178	97
	If yes, can you specify what this would involve?	38	21
15	Does your current surveillance mammography practice differ from how you would ideally like to arrange surveillance mammography?	180	98
16	Can you please indicate how often you would ideally like to arrange surveillance mammography?		
16a	How often would you ideally arrange surveillance mammography for women who have had BCS?	106	58
16b	How often would you ideally arrange surveillance mammography for women who have had mastectomy?	106	58
17	If your current surveillance mammography practice differs from your ideal surveillance mammography practice what factors influence this difference?	53	29
18	Please use this space to provide any comments	63	34

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

Appendix 6

List of NHS trusts of respondents to the survey of UK surveillance mammography practice after the treatment for primary breast cancer

Abertawe Bro Morgannwg University NHS Trust

Barking, Havering & Redbridge NHS Trust

Barts and the London NHS Trust

Basingstoke and North Hampshire NHS Foundation Trust

Royal United Hospital Bath NHS Trust

Bedford Hospital NHS Trust

Belfast Health & Social Care Trust

Blackpool Fylde and Wyre NHS Foundation Trust

Bradford Teaching Hospitals NHS Foundation Trust

Brighton and Sussex University Hospitals NHS Trust

Buckinghamshire Hospitals NHS Trust

Cambridge University Hospitals NHS Foundation Trust

Cardiff and Vale NHS Trust

City Hospitals Sunderland NHS Foundation Trust

Co. Durham and Darlington NHS Foundation Trust

Countess of Chester NHS Foundation Trust

Derby Hospitals NHS Foundation Trust

Doncaster and Bassetlaw Hospitals NHS Foundation Trust

East and North Hertfordshire NHS Trust

East Kent Hospitals University NHS Foundation Trust

Frimley Park Hospital NHS Foundation Trust

George Eliot Hospital NHS Trust

Gloucestershire Hospitals NHS Foundation Trust

Great Western Hospitals NHS Foundation Trust

Gwent Healthcare NHS Trust

Harrogate and District NHS Foundation Trust

Heart of England NHS Foundation Trust

Heatherwood and Wexham Park Hospitals NHS Foundation Trust

Hereford Hospitals NHS Trust

Hinchingbrooke Health Care NHS Trust

Homerton University Hospital NHS Foundation Trust

Hull and East Yorkshire Hospitals NHS Trust

Ipswich Hospital NHS Trust

James Paget University Hospitals NHS Foundation Trust

Kingston Hospital NHS Trust

Leeds Teaching Hospitals NHS Trust

Maidstone and Tunbridge Wells NHS Trust

Mayday Healthcare NHS Trust

Medway NHS Foundation Trust

Mid Cheshire Hospitals NHS Foundation Trust

Mid Yorkshire Hospitals NHS Trust

NHS Ayrshire and Arran

NHS Dumfries and Galloway

NHS Grampian

NHS Greater Glasgow and Clyde

NHS Highland

NHS Lanarkshire

NHS Lothian

NHS Tayside

Noble's Hospital, Isle of Man

Norfolk and Norwich University Hospitals NHS Foundation Trust

North Bristol NHS Trust

North Cumbria University Hospitals NHS Trust

North Wales NHS Trust

North West London Hospitals NHS Trust

North West Wales NHS Trust

Northampton General Hospitals NHS Trust

Northumbria Healthcare NHS Foundation Trust

Nottingham University Hospitals NHS Trust

Oxford Radcliffe Hospitals NHS Trust

Pennine Acute Hospital NHS Trust

Peterborough and Stamford Hospitals Foundation Trust

Plymouth Hospitals NHS Trust

Poole Hospital NHS Trust

Portsmouth Hospitals NHS Trust

Queen Elizabeth Healthcare Trust

Royal Bolton Hospitals NHS Foundation Trust

Royal Cornwall Hospitals NHS Trust

Royal Liverpool and Broadgreen University Hospitals NHS Trust

Royal Surrey County Hospital NHS Trust

Salford Royal NHS Foundation Trust

Sandwell and West Birmingham Hospitals NHS Trust

Sheffield Teaching Hospitals NHS Foundation Trust

Shrewsbury and Telford Hospital NHS Trust

South Devon and Exeter NHS Foundation Trust

South Devon Healthcare NHS Foundation Trust

South London Healthcare NHS Trust, London

South Warwickshire NHS Trust

Southampton University Hospitals NHS Trust

Southern Health and Social Care Trust (Northern Ireland)

Southport and Ormskirk NHS Hospital Trust

St Georges Healthcare NHS Trust

St Helens & Knowsley Hospitals NHS Foundation Trust

Taunton and Somerset NHS Foundation Trust

The Dudley Group of Hospitals NHS Foundation Trust

The Hillingdon Hospital NHS Trust

The Newcastle upon Tyne Hospitals NHS Foundation Trust

The Princess Alexandra Hospital NHS Trust

The Royal Marsden NHS Foundation Trust

The Royal Wolverhampton Hospitals NHS Trust

United Lincolnshire Hospitals NHS Trust

University College London Hospitals NHS Foundation Trust

University Hospital Birmingham NHS Foundation Trust

University Hospital of South Manchester NHS Foundation Trust

University Hospitals Coventry and Warwickshire NHS Trust

University Hospitals of Leicester NHS Trust

University Hospitals of Morecambe Bay NHS Foundation Trust

Walsall Hospitals NHS Trust

Warrington and Halton Hospitals NHS Foundation Trust

West Hertfordshire Hospitals NHS Trust

West Middlesex University Hospital NHS Trust

Winchester and Eastleigh Healthcare NHS Trust

Worcestershire Acute Hospitals NHS Trust

Wrightington, Wigan and Leigh NHS Foundation Trust

York Hospitals NHS Foundation Trust

Appendix 7

Description of mammography surveillance regimens for women following breast-conserving surgery

	Surveillance regimens for women following BCS					
		Frequency (annual, 18-monthly, 2-/3- yearly, annual for 5 years then biennial, other)	Duration			
			Discharge from surveillance mammography follow-up		Discharge from clinical follow-up	
Regimen no.	Initiation: post surgery (months)		Years post surgery	No. of respondents: $n=165$	Years post surgery	No. of respondents: $n=154$
1	6	Annual	10	3	3	1
2	6	Annual	10		5	1
3	6	Annual	10		10	1
4	6	Other	5	1	2	1
5	6	Other	10	2	No	1
6	6	Other	10		10	1
7	8	Annual	10	1	5	1
8	9	Annual	5	1	5	1
9	11	Annual	No	1	5	1
10	11	Annual	10	2	10	2
11	12	Annual	No	32	No	19
12	12	Annual	No		3	1
13	12	Annual	No		5	7
14	12	Annual	No		10	4
15	12	Annual	3	1	3	1
16	12	Annual	5	31	No	4
17	12	Annual	5		2	1
18	12	Annual	5		5	22
19	12	Annual	9	3	5	1
20	12	Annual	10	44	No	2
21	12	Annual	10		3	2
22	12	Annual	10		5	20
23	12	Annual	10		10	18
24	12	Every 18 months	10	6	No	1
25	12	Every 18 months	10		5	4
26	12	Every 18 months	10		10	1
27	12	Every 2 years	No	3	5	2
28	12	Every 2 years	5	3	5	3
29	12	Every 2 years	6	1	No	1
30	12	Every 2 years	9	2	1	2
31	12	Every 2 years	10	4	No	1

Regimen no.	Initiation: post surgery (months)	Frequency (annual, 18-monthly, 2-/3- yearly, annual for 5 years then biennial, other)	Surveillance regimens for women following BCS			
			Duration			
			Discharge from surveillance mammography follow-up		Discharge from clinical follow-up	
			Years post surgery	No. of respondents: $n=165$	Years post surgery	No. of respondents: $n=154$
32	12	Every 2 years	10		1	1
33	12	Every 2 years	10		5	2
34	12	Annual to 5 years then biennial	No	2	5	2
35	12	Annual to 5 years then biennial	5	4	No	1
36	12	Annual to 5 years then biennial	5		3	1
37	12	Annual to 5 years then biennial	5		5	2
38	12	Annual to 5 years then biennial	10	1	5	1
39	12	Annual to 5 years then biennial	11	1	5	1
40	12	Other	No	2	3	1
41		Other	No		5	1
42	12	Other	5	1	5	1
43	12	Other	10	2	3	1
44	12	Other	10		5	1
45	18	Annual	9	1	5	1
46	18	Every 18 months	No	2	No	1
47	18	Every 18 months			5	1
48	18	Every 18 months	5	1	5	1
49	18	Every 18 months	6	2	No	1
50	18	Other	No	1	5	1
51	24	Every 2 years	No	1	6	1
52	24	Every 2 years	5	1	5	1
53	24	Every 2 years	8	1	8	1
54	24	Every 2 years	10	1	10	1

Appendix 8

Description of mammography surveillance regimens for women following mastectomy

	Surveillance regimens for women following mastectomy					
			Duration			
			Discharge from surveillance mammography follow-up		Discharge from clinical follow-up	
Regimen no.	Initiation: post surgery (months)	Frequency (annual, 18-monthly, 2-/ 3-yearly, annual for 5 years then biennial, other)	Years post surgery	No. of respondents: $n=146$	Years post surgery	No. of respondents: $n=136$
1	6	Annual	10	2	3	1
2	6	Annual	10		5	1
3	11	Annual	10	1	10	1
4	12	Annual	10		3	1
5	12	Annual	No	19	No	10
6	12	Annual	No		5	5
7	12	Annual	No		10	4
8	12	Annual	3	1	3	1
9	12	Annual	5	20	No	4
10	12	Annual	5		2	1
11	12	Annual	5		5	13
12	12	Annual	9	2		
13	12	Annual	10	30	No	2
14	12	Annual	10		3	1
15	12	Annual	10		5	11
16	12	Annual	10		10	15
17	12	Every 18 months	No	1	No	1
18	12	Every 18 months	5	1	5	1
19	12	Every 18 months	10	8	No	1
20	12	Every 18 months	10		3	1
21	12	Every 18 months	10		5	5
22	12	Every 18 months	10		10	1
23	12	Every 2 years	No	4	3	1
24	12	Every 2 years	No		5	3
25	12	Every 2 years	5	8	No	1
26	12	Every 2 years	5		5	7
27	12	Every 2 years	9	2	1	2
28	12	Every 2 years	10	9	No	2
29	12	Every 2 years	10		1	1
30	12	Every 2 years	10		5	4
31	12	Every 2 years	10		10	2

	Surveillance regimens for women following mastectomy					
			Duration			
			Discharge from surveillance mammography follow-up		Discharge from clinical follow-up	
Regimen no.	Initiation: post surgery (months)	Frequency (annual, 18-monthly, 2-/3-yearly, annual for 5 years then biennial, other)	Years post surgery	No. of respondents: $n=146$	Years post surgery	No. of respondents: $n=136$
32	12	Every 3 years	5	1	5	1
33	12	Every 3 years	6	1	No	1
34	12	Annual to 5 years then biennial	5	2	3	1
35	12	Annual to 5 years then biennial	5		5	1
36	12	Annual to 5 years then biennial	10	1	5	1
37	12	Annual to 5 years then biennial	11	1	5	1
38	12	Other	No	2	3	1
39	12	Other	No		5	1
40	12	Other	5	1	5	1
41	18	Annual	9	1	5	1
42	18	Every 18 months	No	1	No	1
43	18	Every 18 months	6	2	No	1
44	18	Every 18 months	10	2	5	2
45	18	Every 2 years	No	1	5	1
46	18	Other	No	1	5	1
47	24	Every 2 years	No	6	No	4
48	24	Every 2 years	No		6	1
49	24	Every 2 years	5	5	2	1
50	24	Every 2 years	5		5	3
51	24	Every 2 years	8	1	8	1
52	24	Every 2 years	10	7	3	1
53	24	Every 2 years	10		5	3
54	24	Every 2 years	10		10	2
55	24	Every 3 years	No	1		
56	24	Every 3 years	10	1	10	1

Appendix 9

List of questions used to help define alternative care pathways

For mammographic surveillance:

- For which women is the issue of mammographic surveillance relevant?
- What mammography surveillance should be used?
- Does it vary between women and if so why would it vary?
- How often is it performed?
- Where does it take place?

For clinical follow-up:

- What clinical follow-up is used?
- Does it vary between women and if so why?
- Where does it take place?
- How often?

For unstructured primary care follow-up:

- How might a diagnosis be made?
- At what point would these women enter the care pathway described in *Figures 2–4* (see *Chapter 2*)?

More specifically, what factors might influence the choices made about mammographic surveillance and clinical follow-up?

Other factors to consider:

- age
- risk factors
- type of primary disease
- type of treatment.

Appendix 10

Search strategies: systematic review of clinical effectiveness of surveillance mammography

MEDLINE (1990 – May, week 4, 2009), EMBASE (1990–2009, week 22), MEDLINE In-Process (1 June 2009)

Ovid multifile search: http://shibboleth.ovid.com/

1. exp *breast neoplasms/
2. breast.ti.
3. or/1–2
4. neoplasm recurrence, local/
5. neoplasms, second primary/
6. (recur$ or second or secondary or contralateral or ipsilateral or ibtr or mcbc).tw.
7. or/4–6
8. exp mammography/
9. (mammograph$ or mammogram$).tw.
10. physical examination/
11. breast self-examination/
12. ((physical or clinical or self) adj1 (exam? or examin$)).tw.
13. surveillance.hw,tw.
14. follow up.ti.
15. (routine adj3 (visit or follow up)).tw.
16. or/8–15
17. exp clinical trial/
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomization/use emez
21. randomi?ed.ab.
22. randomly.ab.
23. trial.ab.
24. groups.ab.
25. comparative study/use mesz
26. follow-up studies/use mesz
27. time factors/use mesz
28. Treatment outcome/use emez
29. major clinical study/use emez
30. controlled study/use emez
31. clinical trial/use emez
32. (chang$ or evaluat$ or reviewed or baseline).tw.
33. (prospective$ or retrospective$).tw.
34. (cohort$ or case series).tw.
35. (compare$ or compara$).tw.
36. or/17–35
37. human/
38. 36 and 37

39. 3 and 7 and 16 and 38
40. limit 39 to yr="1990 – 2009"
41. remove duplicates from 40

Science Citation Index (1990 – 3 June 2009), BIOSIS (1990 – 4 June 2009)

ISI Web of Knowledge: http://wok.mimas.ac.uk/

1 TS=(breast neoplasm* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc)) AND Document Type=(Article)

2 TS=(breast cancer* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc)) AND Document Type=(Article)

3 TS=(breast carcin* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc)) AND Document Type=(Article)

4 TS=(breast tumour* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc)) AND Document Type=(Article)

5 TS=(breast tumor* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc)) AND Document Type=(Article)

6 #1 or #2 or #3 or #4 or #5 AND Document Type=(Article)

7 #6 and TS=mammogram* AND Document Type=(Article)

8 #6 and TS=mammograph* AND Document Type=(Article)

9 #6 and TS=surveillance AND Document Type=(Article)

10 #6 and TS=routine AND Document Type=(Article)

11 TS="physical exam*" AND Document Type=(Article)

12 #6 AND #11 AND Document Type=(Article)

13 TS="self exam*" AND Document Type=(Article)

14 #6 and #13 AND Document Type=(Article)

15 TS="clinical exam* " AND Document Type=(Article)

16 #6 and #15 AND Document Type=(Article)

17 TI="follow up" AND Document Type=(Article)

18 #6 and #17 AND Document Type=(Article)

19 #18 OR #16 OR #14 OR #12 OR #10 OR #9 OR #8 OR #7

20 TI=breast AND Document Type=(Article)

21 #19 and #20 AND Document Type=(Article)

Cochrane Library Issue 2, 2009 (Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews)

www3.interscience.wiley.com/

#1 MeSH descriptor Breast Neoplasms explode all trees

#2 (breast):ti

#3 (#1 OR #2)

#4 MeSH descriptor Neoplasm Recurrence, Local explode all trees

#5 MeSH descriptor Neoplasms, Second Primary explode all trees

#6 (recur* or second or secondary):ti,ab,kw or (contralateral or ipsilateral):ti,ab,kw or (ibtr or mcbc):ti,ab,kw

#7 (#4 OR #5 OR #6)

#8 MeSH descriptor Mammography explode all trees

#9 (mammograph* or mammogram*):ti,ab,kw

#10 MeSH descriptor Physical Examination, this term only

#11 MeSH descriptor Breast Self-Examination, this term only

#12 (follow up):ti

#13 (routine near/3 visit*):ti,ab,kw or (routine near/3 follow up):ti,ab,kw

#14 (physical near/1 exam*):ti,ab,kw or (clinical near/1 exam*):ti,ab,kw or (self near/1 exam*):ti,ab,kw

#15 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)

#16 (#3 AND #7 AND #15)

CANCERLIT (3 June 2009)

The US National Library of Medicine: www.ncbi.nlm.nih.gov

#1 Search (breast neoplasms[majr] AND human[mh] AND english[la]) OR dcis[ti] OR lcis[ti] OR ((breast[ti] OR breasts[ti] OR mammary[ti] OR nipple[ti] OR nipples[ti]) AND ((cancer*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR malignan*[ti] OR tumor*[ti] OR tumour*[ti] OR neoplasm*[ti]) OR in situ[ti]))

#2 Search recur* or secondary or contralateral or ipsilateral or ibtr or mcbc Limits: Cancer

#3 Search #1 and #2 Limits: Cancer

#4 Search (("mammogram* "[Title]) OR ("examin*"[Title]))

#5 Search (("surveillance"[Title]) OR ("follow up"[Title]) OR ("routine visit*" [Title]))

#6 #4 OR #5

#7 #3 AND #6

The Health Technology Assessment/Database of Abstracts of Reviews and Effects/NHS Economic Evaluation databases, June 2009

Centre for Reviews and Dissemination: http://nhscrd.york.ac.uk/welcome.htm

1 MeSH Breast Neoplasms EXPLODE 1 2

2 MeSH Mammography EXPLODE 1

3 mammography OR mammogram

4 MeSH Population Surveillance EXPLODE 1 2 3 4

5 surveillance OR monitor*

6 #2 or #3 or #4 or #5

7 #1 and #6

8 MeSH Postoperative Care EXPLODE 1 2 3

9 MeSH Follow-Up Studies EXPLODE 1 2 3

10 MeSH Neoplasm Recurrence, Local EXPLODE 1 2

11 MeSH Recurrence EXPLODE 1

12 recurrence OR secondary OR ipsilateral OR contralateral

13 #8 OR #9 OR #10 OR #11 OR #12

14 #7 AND #13

15 "follow-up strategies"

16 follow AND up

17 "follow up"

#18 #15 OR #16 OR #17

19 #13 or #18

20 #7 AND #19

Clinical Trials, June 2009

http://clinicaltrials.gov/ct/gui/c/r

"breast diseases" AND (mammography OR surveillance)

Current Controlled Trials, June 2009

www.controlled-trials.com/

breast AND (mammography OR surveillance)

The World Health Organization International Clinical Trials Registry Platform, June 2009

World Health Organization: www.who.int/ictrp/en/

breast AND mammography OR breast AND surveillance

National Research Register Archive

National Institute for Health Research portal: https://portal.nihr.ac.uk/Pages/NRRArchiveSearch.aspx

NIHR portfolio, June 2009

National Institute for Health Research portal: https://portal.nihr.ac.uk/Search/Advanced.aspx

breast AND mammography OR breast AND surveillance

National Cancer Institute Clinical Trials, June 2009

The US National Institutes of Health: www.cancer.gov

breast cancer (female) AND mammography OR surveillance

Websites consulted

American College of Radiology
www.acr.org/

American Society of Breast Disease
www.asbd.org/

American Society of Clinical Oncology
www.asco.org/

Breast Cancer Surveillance Consortium
http://breastscreening.cancer.gov/

CancerWEB
www.infoventures.com/cancer/

Canadian Task Force on Preventive Health Care
www.ctfphc.org/

Cancer Research UK
www.cancerresearchuk.org/

European Society for Medical Oncology
www.esmo.org/

National Breast and Ovarian Cancer Centre
www.nbocc.org.au

National Cancer Institute
www.cancer.gov/cancertopics/types/breast

National Comprehensive Cancer Network
www.nccn.org/index.asp

National Library for Health
www.library.nhs.uk/default.aspx

Royal College of Radiologists
www.rcr.ac.uk/

Surveillance, Epidemiology, and End Results Program
http://seer.cancer.gov/

Appendix 11

Reports of included studies: systematic review of clinical effectiveness of surveillance mammography

Churn 2001

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Lash 2005

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Lash 2006

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Lash 2007

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Montgomery 2007

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Montgomery 2009

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Paszat 2008

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Appendix 12

Excluded studies: systematic review of clinical effectiveness of surveillance mammography

Surveillance regimens not included (n = 76)

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Appendix 13

Data extraction form for the systematic review of clinical effectiveness of surveillance mammography

HTA Mammography Surveillance – Clinical Effectiveness Review 1 data extraction form
Version 3   11 December 2008

Study id:	**Extractor initials:**

Date:

Study ids of linked reports:

Aim of study:

Study design:
- ☐   *RCT*
- ☐   *Non-randomised comparison*
- ☐   **Prospective/Retrospective cohort** (please underline)

Multicentre study?   ☐   Yes   *If Yes number of centres:*
                         ☐   **No**

Length of follow-up:

Study start/end dates: **Duration of study:**

Country:

Source of funding:

Additional information on study design:

Types of participants:

☐   **Women without detectable metastatic disease who have received breast conserving surgery for primary breast cancer**

☐   **Women without detectable metastatic disease who have received mastectomy for primary breast cancer**

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Type of Intervention /Comparator

RCT/Comparison Studies
- ☐ **SM versus No formal direction or contact with a health care professional**
- ☐ **SM versus Alternative follow up regimen** (please state regime)
- ☐ **Differences in frequency of SM regimens**

Cohorts:
- ☐ **Surveillance Mammography**
- ☐ **Alternative follow up regimen** (please state regimen)

Outcomes reported:

☐ **IBTR**

- ☐ **Overall survival**
- ☐ **Disease free survival**
- ☐ **QOL**
- ☐ **Harms of mammography**
- ☐ **Uptake of mammography**

☐ **MCBC**

- ☐ **Overall survival**
- ☐ **Disease free survival**
- ☐ **QOL**
- ☐ **Harms of mammography**
- ☐ **Uptake of mammography**

Participant Characteristics

Study inclusion criteria:

Study exclusion criteria:

	Group 1	Group 2	Group 3	All
No Enrolled				
[comparison studies] No randomised/allocated				
No received intervention				
[RCTs] No of Post randomisation exclusions				
No Analysed				
No Lost to follow-up/withdrawn				
No Age: Mean 　*Median* 　*SD* 　*Range* 　**No <50** 　**No 50 and over**				
Hormone Receptor Status **No ER +** **No ER –** **No PR +** **No PR –**				

No HER2 + **No HER2 –**				
NPI Status **No Low Risk (NPI<3.4)** **No Medium Risk (NPI 3.4–5.4)** **No High Risk (NPI>5.4)**				
Genetic Status				
No Depcat Score: **1** **2** **3** **4** **5** **6** **7** Please record other socio-economic factors in additional patient information				
Primary Treatment: **No received primary breast conserving surgery (WLE)**				
No received primary mastectomy				
No reconstructed breast				
Primary Tumour Characteristics: **No DCIS** **No LCIS** **No Invasive** **Grade 1** **Grade 2** **Grade 3** **Size** **No Lymph Node Status +** **No Lymph Node Status –**				
Nos receiving treatment for primary breast cancer **Neoadjuvant radiotherapy** **Neoadjuvant chemotherapy** **Adjuvant radiotherapy** **Adjuvant chemotherapy** **Adjuvant tamoxifen /Endocrine** **Oopherectomy or ovarian ablation**				

Primary tumour excision margins: **No clear margins** **No unclear margins**				
Additional patient information:				

Intervention Group – Group 1

Components of the Intervention

Component 1

☐   **Surveillance Mammography**
☐   **Unstructured Primary Care Follow Up**
☐   **Structured Primary Care Follow Up**
☐   **Specialist led Clinical Exam**
☐   **Healthcare Professional directed self-exam**
☐   **Alternative surveillance regimen** (please state)

Intervention Setting
☐   **Secondary Care**
☐   **Primary Care**
☐   **Other** (please state)

Who administered the intervention? (please give experience level if recorded)
☐   **Radiologist**
☐   **Hospital Clinician**
☐   **Breast Care Nurse**
☐   **Patient**
☐   **Other** (please state)

How long after primary treatment/at what time point was the intervention (or component 1 of the intervention) initiated?

Frequency of the intervention:

Duration of the intervention:

Components of the Intervention

Component 2

- ☐ **Surveillance Mammography**
- ☐ **Unstructured Primary Care Follow Up**
- ☐ **Structured Primary Care Follow Up**
- ☐ **Specialist led Clinical Exam**
- ☐ **Healthcare Professional directed self-exam**
- ☐ **Alternative surveillance regimen** (please state)

Intervention Setting
- ☐ **Secondary Care**
- ☐ **Primary Care**
- ☐ **Other** (please state)

Who administered the intervention? (please give experience level if recorded)
- ☐ **Radiologist**
- ☐ **Hospital Clinician**
- ☐ **Breast Care Nurse**
- ☐ **Patient**
- ☐ **Other** (please state)

How long after primary treatment/at what time point was the intervention (or component 2 of the intervention) initiated?

Frequency of the intervention:

Duration of the intervention:

Components of the Intervention

<u>Component 3</u>

- ☐ **Surveillance Mammography**
- ☐ **Unstructured Primary Care Follow Up**
- ☐ **Structured Primary Care Follow Up**
- ☐ **Specialist led Clinical Exam**
- ☐ **Healthcare Professional directed self-exam**
- ☐ **Alternative surveillance regimen** (please state)

Intervention Setting
- ☐ **Secondary Care**
- ☐ **Primary Care**
- ☐ **Other** (please state)

Who administered the intervention? (please give experience level if recorded)
- ☐ **Radiologist**
- ☐ **Hospital Clinician**
- ☐ **Breast Care Nurse**
- ☐ **Patient**
- ☐ **Other** (please state)

How long after primary treatment/at what time point was the intervention (or component 3 of the intervention) initiated?

Frequency of the intervention:

Duration of the intervention:

Please use a separate sheet for any additional Group 1 intervention components.

Comparison Group – Group 2

Components of the Comparator

Component 1

- ☐ **Surveillance Mammography**
- ☐ **Unstructured Primary Care Follow Up**
- ☐ **Structured Primary Care Follow Up**
- ☐ **Specialist led Clinical Exam**
- ☐ **Healthcare Professional directed self-exam**
- ☐ **Alternative surveillance regimen** (please state)

Comparator Setting
- ☐ **Secondary Care**
- ☐ **Primary Care**
- ☐ **Other** (please state)

Who administered the comparator? (please give experience level if recorded)
- ☐ **Radiologist**
- ☐ **Hospital Clinician**
- ☐ **Breast Care Nurse**
- ☐ **Patient**
- ☐ **Other** (please state)

How long after primary treatment/at what time point was the comparator (or component 1 of the comparator) initiated?

Frequency of the comparator:

Duration of the comparator:

Components of the Comparator

Component 2

- ☐ **Surveillance Mammography**
- ☐ **Unstructured Primary Care Follow Up**
- ☐ **Structured Primary Care Follow Up**
- ☐ **Specialist led Clinical Exam**
- ☐ **Healthcare Professional directed self-exam**
- ☐ **Alternative surveillance regimen** (please state)

Intervention Setting
- ☐ **Secondary Care**
- ☐ **Primary Care**
- ☐ **Other** (please state)

Who administered the intervention? (please give experience level if recorded)
- ☐ **Radiologist**
- ☐ **Hospital Clinician**
- ☐ **Breast Care Nurse**
- ☐ **Patient**
- ☐ **Other** (please state)

How long after primary treatment/at what time point was the comparator (or component 2 of the comparator) initiated?

Frequency of the comparator:

Duration of the comparator:

Components of the Comparator

Component 3

☐ **Surveillance Mammography**
☐ **Unstructured Primary Care Follow Up**
☐ **Structured Primary Care Follow Up**
☐ **Specialist led Clinical Exam**
☐ **Healthcare Professional directed self-exam**
☐ **Alternative surveillance regimen** (please state)

Intervention Setting
☐ **Secondary Care**
☐ **Primary Care**
☐ **Other** (please state)

Who administered the comparator? (please give experience level if recorded)
☐ **Radiologist**
☐ **Hospital Clinician**
☐ **Breast Care Nurse**
☐ **Patient**
☐ **Other** (please state)

How long after primary treatment/at what time point was the comparator (or component 3 of the comparator) initiated?

Frequency of the comparator:

Duration of the comparator:

Please use a separate sheet for any additional Group2 comparator components.

Comparison Group – Group 3

Components of the Comparator

Component 1

- ☐ **Surveillance Mammography**
- ☐ **Unstructured Primary Care Follow Up**
- ☐ **Structured Primary Care Follow Up**
- ☐ **Specialist led Clinical Exam**
- ☐ **Healthcare Professional directed self-exam**
- ☐ **Alternative surveillance regimen** (please state)

Comparator Setting
- ☐ **Secondary Care**
- ☐ **Primary Care**
- ☐ **Other** (please state)

Who administered the comparator? (please give experience level if recorded)
- ☐ **Radiologist**
- ☐ **Hospital Clinician**
- ☐ **Breast Care Nurse**
- ☐ **Patient**
- ☐ **Other** (please state)

How long after primary treatment/at what time point was the comparator (or component 1 of the comparator) initiated?

Frequency of the comparator:

Duration of the comparator:

Components of the Comparator

Component 2

    ☐   **Surveillance Mammography**
    ☐   **Unstructured Primary Care Follow Up**
    ☐   **Structured Primary Care Follow Up**
    ☐   **Specialist led Clinical Exam**
    ☐   **Healthcare Professional directed self-exam**
    ☐   **Alternative surveillance regimen** (please state)

Intervention Setting
    ☐   **Secondary Care**
    ☐   **Primary Care**
    ☐   **Other** (please state)

Who administered the intervention? (please give experience level if recorded)
    ☐   **Radiologist**
    ☐   **Hospital Clinician**
    ☐   **Breast Care Nurse**
    ☐   **Patient**
    ☐   **Other** (please state)

How long after primary treatment/at what time point was the comparator (or component 2 of the comparator) initiated?

Frequency of the comparator:

Duration of the comparator:

Components of the Comparator

Component 3

☐   **Surveillance Mammography**
☐   **Unstructured Primary Care Follow Up**
☐   **Structured Primary Care Follow Up**
☐   **Specialist led Clinical Exam**
☐   **Healthcare Professional directed self-exam**
☐   **Alternative surveillance regimen** (please state)

Intervention Setting
☐   **Secondary Care**
☐   **Primary Care**
☐   **Other** (please state)

Who administered the comparator? (please give experience level if recorded)
☐   **Radiologist**
☐   **Hospital Clinician**
☐   **Breast Care Nurse**
☐   **Patient**
☐   **Other** (please state)

How long after primary treatment/at what time point was the comparator (or component 3 of the comparator) initiated?

Frequency of the comparator:

Duration of the comparator:

Please use a separate sheet for any additional intervention components.

Outcome(s) reported and time point(s)

How were outcome data collected/measured?

Did the analysis adjust for any confounding factors (if yes please state the confounding factor(s)?

How was the confounding factor categorised? (e.g. Age, <50 or 50>)

Outcome	Time Reported Please record for all reported time points e.g. Year 1, year 2, year 3, etc.	Group 1	Group 2	Group 3	*All*
Hazard Ratio (as reported by publication)					
Median Time to Event					
No. Overall Survival					
Alive					
Dead					
No. Disease free survival (without IBTR)					
Nos with IBTR					

No. Disease free survival (without MCBC)					
Nos with MCBC					
No. Attending/ Uptake of mammography					

Quality of life				
Measure used	*Group 1*	*Group 2*	*Group 3*	*Notes*

Adverse events				

General information on adverse events:

No. Adverse events reported & Type of Event	*Group 1*	*Group 2*	*Group 3*	*All*

Additional study information:

HTA Mammography Surveillance – Clinical Effectiveness Review 1
Data Extraction Form for Outcomes by Subgroup

Version 2   **09 December 08**

Study ID   **Extractor's Initials**   **Date**

List of possible subgroups:

Grade of primary breast cancer tumour, Size of primary breast cancer tumour, Lymphovascular Invasion, NPI status, ER/PR/HER2 status, Genetic status (BRCA genes), *Age* (Under 50 years, 50 years and over), *Type and extent of surgery for primary breast cancer tumour (*Breast conserving, Mastectomy, Excision margins), *Primary neoadjuvant / adjuvant treatment (*Radiotherapy, Chemotherapy, Tamoxifen/Endocrine treatment, Oopherectomy or ovarian ablation) Depcat status

Outcome	Subgroup Please write below.	Time Reported Please record for all reported time points e.g. Year 1, year 2, year 3, etc.	Group 1	Group 2	Group 3	*All*
Hazard Ratio (as reported by publication)						
Median Time to Event						

Outcome	Subgroup Please write below.	Time Reported Please record for all reported time points e.g. Year 1, year 2, year 3, etc.	Group 1	Group 2	Group 3	*All*
No. Overall Survival **Nos Alive**						
Nos Dead						

Outcome	Subgroup Please write below.	Time Reported Please record for all reported time points e.g. Year 1, year 2, year 3, etc.	Group 1	Group 2	Group 3	*All*
No. Disease free survival **Nos without IBTR**						
Nos with IBTR						

Outcome	Subgroup Please write below.	Time Reported Please record for all reported time points e.g. Year 1, year 2, year 3, etc.	Group 1	Group 2	Group 3	*All*
Nos without MCBC						
Nos with MCBC						

Outcome	Subgroup Please write below.	Time Reported Please record for all reported time points e.g. Year 1, year 2, year 3, etc.	Group 1	Group 2	Group 3	*All*
No Attending/ **Uptake of** **mammography**						
Quality of Life (state Measure used)						
Adverse Events (give details)						

Appendix 14

Quality assessment tool used in the systematic review of clinical effectiveness of surveillance mammography

HTA mammography surveillance – clinical effectiveness and cost-effectiveness review 1

Checklist for quality assessment of non-randomised studies (comparative and cohort studies). Items specific to comparative studies are in italic text.

Version 3   May 2010

Study ID: Reviewer initials: Date:

Criteria	Yes	No	Unclear	Comments
Participants: sample definition and selection				
1. Were participants a representative sample selected from a relevant patient population?				
2. Were the inclusion/exclusion criteria of participants clearly described?				
3. Were participants entering the study at a similar point in their disease progression?				
4. Was selection of patients consecutive?				
5. Was data collection undertaken prospectively?				
6. Were the groups comparable on demographic characteristics and clinical features?				
Intervention				
7. Was the intervention clearly defined?				
8. Was the comparison clearly defined?				
Outcome measures				
9. Were overall survival, disease-free survival and relative survival outcomes considered?				
10. Were objective (valid and reliable) outcome measure/s used for ascertaining disease-free survival?				
11. Was the assessment of disease-free outcomes blind?				

Criteria	Yes	No	Unclear	Comments
Follow-up				
12. Was follow-up long enough to detect important effects on outcomes of interest? Follow-up must be a minimum of 5 years to account for changes in surveillance policy after this time due to most recurrences occurring within first 5 years following initial breast cancer				
13. Was information provided on non-respondents, dropouts?				
14. Were participants lost to follow-up likely to introduce bias? (e.g. high dropout rate, differential dropout, no description of those lost)				
15. Was length of follow-up similar between comparison groups?				
Analysis				
16. Were important prognostic factors identified?				
17. Were the analyses adjusted for confounding factors? Importance of confounding factor as judged by study authors?				
18. Did authors attempt to correct for lead time bias?				
19. Did authors attempt to correct for length time bias?				

Appendix 15

Characteristics of the studies included in the systematic review of clinical effectiveness of surveillance mammography

Study ID	Participants	Description of surveillance regimen	Study comparator	Outcomes summary[a]
Churn 2001[53] *Study design*: retrospective cohort *Follow-up*: 5 years *Primary treatment*: all 1993 *Country*: UK	*Enrolled*: $n=612$ *Excluded*: $n=0$ *Analysed*: $n=612$ *Mastectomy*: $n=104$ analysed *BCS*: $n=505$ analysed *No primary surgery*: $n=3$ analysed *Age (years)*: Mean NR, SD NR, range NR <50 years $n=189$ 50 years and over $n=423$	Clinical examination 3- to 4-monthly for first 2–3 years, 6-monthly for up to 5 years, annually thereafter. System involved alternate appointments with the surgical and oncological teams for 3–5 years, followed by discharge to continue follow-up in one or other of these clinics. Surveillance mammography according to individual clinician preference (usually less frequently than annually)	None	*Type of recurrence*: local recurrence (IBTR and MCBC?) *Local recurrence at 5 years post primary treatment*: BCS (IBTR) $n=25$ (four concurrent with metastases, two after presentation with systemic disease) Mastectomy (MCBC): $n=9$ (three concurrent metastases) *Overall survival at 5 years*: Alive all $n=500$ Alive breast cancer recurrence NR Dead all cause $n=112$ Dead breast cancer NR Dead breast cancer recurrence NR *Mode of detection*: IBTR: SM $n=7$ CE $n=8$ Symptomatic interim referral $n=9$ MCBC: CE $n=6$ Symptomatic interim referral $n=1$ Uncertain $n=2$
Lash 2005[59] *Study design*: multicentre prospective cohort *Follow-up*: median 7.4 years, range 10 months to 9.5 years *Primary treatment*: October 1992 to March 1994 *Country*: USA	*Enrolled*: $n=388$ *Excluded*: $n=85$ *Analysed*: $n=303$ *Mastectomy*: $n=71$ analysed *BCS*: $n=228$ analysed *Primary surgery details missing*: $n=4$ analysed *Age (years)*: Mean NR, SD NR, range NR <50 years $n=0$ 50 years and over $n=388$	Guideline surveillance – defined as annual CE and XRM for patients with asymptomatic history	Number of consecutive years of receipt of guideline surveillance compared with not receiving guideline surveillance	*Recurrence*: NR *Overall survival*: Alive all $n=240$ Alive breast cancer recurrence NR Dead (all cause) $n=63$ Dead breast cancer $n=27$ Dead other $n=36$ Dead breast cancer recurrence NR

Study ID	Participants	Description of surveillance regimen	Study comparator	Outcomes summary[a]
Lash 2006[60] *Study design*: multicentre prospective cohort *Follow-up*: follow-up time began 182 days after surgery or 90 days after completing radiation therapy or chemotherapy, whichever came latest; follow-up time ended on the date of death, the date upon which the last surveillance form was returned from a physician's office or 30 April 2004, whichever came first *Primary treatment*: 1 December 1996 to 30 September 1999 Country: USA	*Enrolled*: $n = 865$ *Excluded*: $n = 531$ *Analysed*: $n = 334$ *Mastectomy*: analysed $n = 161$ *BCS*: analysed $n = 168$ *Primary surgery details missing*: analysed $n = 5$ *Age (years)*: Mean NR, SD NR, range NR < 50 years $n = 0$ 50 years and over $n = 865$	Presumed guideline surveillance – defined as annual examination for patients with asymptomatic history, physical examination and XRM	Number of XRMs received by women who died (all-cause mortality) compared with the number of XRMs received by women who did not die	*Recurrence*: NR *Overall survival*: Alive all $n = 302$ Alive breast cancer recurrence NR Dead all cause $n = 32$ Dead breast cancer $n = 13$ Dead other $n = 19$ Dead breast cancer recurrence NR
Lash 2007[58] *Study design*: retrospective cohort *Follow-up*: 5 years *Primary treatment*: 1990–4 *Country*: USA	*Enrolled*: $n = 1846$ *Excluded*: NR *Analysed*: 812 *Mastectomy*: enrolled $n = 973$, analysed $n = 537$ *BCS*: enrolled $n = 851$, analysed 273 *Other surgery*: enrolled $n = 22$, analysed $n = 2$ *Age (years)*: Mean NR, SD NR, range NR < 50 years $n = 0$ 50 years and over $n = 1846$	Presumed guideline surveillance – defined as annual examination for patients with asymptomatic history, physical examination and XRM	Number of XRMs received by women who died (all-cause mortality) compared with the number of XRMs received by women who did not die	*Type of recurrence*: local (IBTR) and locoregional and distant Locoregional and distant recurrence at 5 years $n = 231$ IBTR recurrence $n = 37$ *Overall survival at 5 years*: Alive NR Dead all cause $n = 391$ Dead breast cancer $n = 178$ Dead breast cancer recurrence $n = 130$, local recurrence $n = 37$ Dead other causes $n = 213$

Study ID	Participants	Description of surveillance regimen	Study comparator	Outcomes summary[a]
Montgomery 2007[54] *Study design*: retrospective cohort *Follow-up*: median 10 years, range 1.5–15 years *Primary treatment*: 1991–8 *Country*: UK	*Enrolled*: $n = 1312$ *Excluded*: $n = 42$ *Analysed*: $n = 110$ *Mastectomy*: $n = 0$ *BCS*: enrolled $n = 1312$, analysed $n = 110$ *Age (years)*: Mean 56, SD NR, range 24–91 < 50 NR 50 and over NR	Outpatient clinical examination performed 3- to 4-monthly for first 2 years, 6-monthly for 3 years then annually until 10 years post primary treatment from 1991 to 1998. From 2000, all patients received annual clinic visits only. Annual bilateral surveillance mammography performed. All patients received instruction in breast self-examination. Additional interval visits arranged as required	None	*Type of recurrence*: local recurrence (IBTR) and contralateral second primary cancer (MCBC) *Recurrence at 5 years*: IBTR $n = 48$ MCBC $n = 35$ Bilateral IBTR + MCBC $n = 2$ Ipsilateral axilla $n = 25$ *Overall survival at 5 years*: Alive all NR Dead breast cancer recurrence $n = 24$ Dead IBTR recurrence $n = 15$ Dead MCBC $n = 8$ Dead bilateral $n = 1$ Dead other NR [b]*Mode of detection*:[6] IBTR: SM $n = 25$ (6 died) CE $n = 4$ (4 died) Symptomatic interim referral $n = 12$ (4 died) Symptoms $n = 5$ (1 died) MCBC: SM $n = 25$ (5 died) CE $n = 2$ Symptomatic interim referral $n = 5$ (1 died) Symptoms $n = 3$ (2 died) Bilateral IBTR/MCBC: SM $n = 2$ (1 died)

Study ID	Participants	Description of surveillance regimen	Study comparator	Outcomes summary[a]
Montgomery 2009[55] *Study design*: retrospective cohort *Follow-up*: median 5.9 years, range 4 months to 10.5 years *Primary treatment*: October 1995 to September 2001 *Country*: UK	*Enrolled*: $n = 198$ *Excluded*: $n = 2$ *Analysed*: $n = 196$ *Mastectomy*: $n = 0$ *BCS*: enrolled $n = 198$, analysed $n = 196$ *Age (years)*: Mean 58 years, median NR, SD 13.6 years, range 28–91 years < 50 NR 50 and over NR	Outpatient clinical examination performed 3- to 4-monthly for first 2 years, 6-monthly for 3 years, annual visits until 10th anniversary thereafter. From 2000 all patients received annual clinic visits. Additional interval visits arranged as required. Annual bilateral surveillance mammography performed. Patients usually discharged to the national breast-screening unit at 10 years	Survival for CE-detected tumour compared with survival for XRM-detected tumour	*Type of recurrence*: local recurrence (IBTR), axilla recurrence and contralateral second primary (MCBC) Local recurrence at 1 year: IBTR $n = 0$, MCBC $n = 1$ Local recurrence 1–3 years: IBTR $n = 1$, MCBC $n = 1$, ipsilateral axilla $n = 1$ Local recurrence > 3 years: IBTR $n = 3$, MCBC $n = 4$, ipsilateral axilla $n = 1$ Total recurrence: IBTR $n = 4$, MCBC $n = 6$, ipsilateral axilla $n = 2$ *Overall survival*: Alive all NR Dead all cause NR Alive breast cancer NR Alive breast cancer recurrence NR Dead breast cancer NR Dead breast cancer recurrence NR *Mode of detection*: IBTR: CE $n = 1$ MCBC: SM $n = 3$ CE $n = 2$ *Locoregional relapse*: Symptomatic interim referral $n = 2$
Paszat 2008[56] *Study design*: retrospective cohort (random sample) *Follow-up*: Recurrence 1991–2004 Vital status 1991–2006 ≥ 1 SM episode in days: 25th percentile:1631 50th percentile: 4287 75th percentile: 5011 No episode SM in days: 25th percentile:440 50th percentile: 891 75th percentile: 1849 *Primary treatment*: 1991–1993 *Country*: Canada	*Enrolled*: $n = 1600$ (> 1 episode SBS $n = 1200$; no SBS $n = 400$) *Excluded*: $n = 699$ (> 1 episode SBS $n = 609$; no SBS $n = 490$) *Analysed*: $n = 901$ *Mastectomy*: $n = 317$ *BCS*: $n = 584$ *Age (years)*: Mean NR, SD NR, range NR < 50 $n = 255$ 50 and over $n = 646$	Presumed guideline surveillance – defined as annual CE and XRM for patients with asymptomatic history	Number of XRMs received compared with no receipt of XRM	*Type of recurrence*: local recurrence (IBTR) and contralateral second primary cancer (MCBC) Recurrence events: IBTR $n = 84$ MCBC $n = 49$ *Overall survival*: Alive $n = 389$ Dead breast cancer $n = 374$ Dead other causes $n = 138$ *Mode of detection*: IBTR: SM $n = 33$ Other $n = 51$ MCBC: SM $n = 24$ Other $n = 25$

Study ID	Participants	Description of surveillance regimen	Study comparator	Outcomes summary[a]
Yau 2008[57] *Study design*: retrospective cohort *Follow-up*: median 5.9 years, range 0.2–13 years *Primary treatment*: 1994–2003 *Country*: Hong Kong	*Enrolled*: $n = 507$ *Excluded*: $n = 0$ *Analysed*: $n = 507$ *Mastectomy*: $n = 0$ *BCS*: $n = 507$ *Age (years)*: Median 46, SD NR, range 25–90 <50 NR 50 and over NR	Clinical examination every 2–3 months in the first 2 years, every 4–6 months in the third to fifth years, annually thereafter. Bilateral surveillance mammography performed annually first 5 years, once every 1–2 years for next 5 years. Supplementary ultrasound performed at clinician's discretion	None	*Type of recurrence*: local recurrence (IBTR) and contralateral second primary cancer (MCBC) Recurrence events: IBTR $n = 23$ MCBC $n = 13$ *Overall survival*: Alive all NR Alive breast cancer recurrence NR Dead all cause NR Dead breast cancer NR Dead breast cancer recurrence NR *Mode of detection*: IBTR: SM $n = 10$ CE $n = 8$ Symptomatic interim referral $n = 2$ Supplementary ultrasound $n = 2$ MCBC: SM $n = 8$ CE $n = 3$ Symptomatic interim referral $n = 1$ Supplementary ultrasound $n = 1$

CE, clinical examination; SBS, subsequent breast surgery; SM, surveillance mammography; XRM, X-ray mammography.

a   The included studies did not include data on the following outcomes considered in our review: quality of life, harms of mammography (adverse events), uptake of mammography, economic outcomes.

b   Two patients with IBTR were excluded from mode of detection data by the study authors. Both were diagnosed incidentally during breast reshaping procedures. Both patients subsequently died.

Appendix 16

Quality assessment of individual studies included in the systematic review of clinical effectiveness of surveillance mammography

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19
Chum 2001[53]	+	+	+	?	–	NA	+	NA	+	+	NA	+	?	?	NA	+	NA	–	–
Lash 2005[59]	–	+	+	+	+	NA	+	+	+	+	NA	+	+	–	NA	+	NA	–	–
Lash 2006[60]	–	+	+	+	+	NA	+	NA	+	+	NA	+	+	–	NA	+	NA	–	–
Lash 2007[58]	–	+	+	?	–	NA	+	NA	+	+	NA	+	?	?	NA	+	NA	–	–
Montgomery 2007[54]	+	+	+	+	–	NA	+	NA	+	+	NA	+	+	–	NA	+	NA	–	–
Montgomery 2009[55]	+	+	+	?	–	NA	+	NA	+	+	NA	+	+	–	NA	–	NA	NA	NA
Paszat 2008[56]	–	+	+	?	–	NA	+	NA	+	+	NA	+	?	?	NA	+	NA	–	–
Yau 2008[57]	+	+	+	?	–	NA	+	NA	+	+	NA	+	?	?	NA	+	NA	N/A	N/A

NA, not applicable; +, yes to the question; ?, unclear; –, no to the question.

Appendix 17

Search strategies: systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

MEDLINE (1990 – March, week 1, 2009), EMBASE (1990–2009, week 11)
MEDLINE In-Process (13 March 2009)

Ovid multifile search: https://shibboleth.ovid.com/

1. exp *breast neoplasms/use mesz
2. exp *breast tumor/use emez
3. breast.ti.
4. or/1–3
5. neoplasm recurrence, local/use mesz
6. tumor recurrence/use emez
7. cancer recurrence/use emez
8. neoplasms, second primary/use mesz
9. second cancer/use emez
10. (recur$ or second or secondary or contralateral or ipsilateral or ibtr or mcbc).tw.
11. or/5–10
12. exp mammography/
13. (mammograph$ or mammogram$).tw.
14. physical examination/
15. breast self-examination/
16. breast examination/use emez
17. ((physical or clinical or self) adj1 (exam? or examin$)).tw.
18. surveillance.hw,tw.
19. follow up.ti.
20. (routine adj3 (visit or follow up)).tw.
21. Magnetic resonance imaging/use mesz
22. Nuclear Magnetic resonance imaging/use emez
23. (magnetic resonance imag$ or mri).tw.
24. ultrasonography, mammary/use mesz
25. echomammography/use emez
26. (ultrasound or ultrasonograph$ or echo mammogra$or echomammogra$).tw.
27. or/12–26
28. neoplasm recurrence, local/di use mesz
29. tumor recurrence/di use emez
30. cancer recurrence/di use emez
31. neoplasms, second primary/di use mesz
32. second cancer/di use emez
33. or/28–32
34. 4 and 33
35. "sensitivity and specificity"/
36. roc curve/

37. receiver operating characteristic/use emez
38. predictive value of tests/
39. diagnostic errors/use emez
40. false positive reactions/use mesz
41. false negative reactions/use mesz
42. diagnostic accuracy/use emez
43. diagnostic value/use emez
44. du.fs. use mesz
45. sensitivity.tw.
46. distinguish$.tw.
47. differentiat$.tw.
48. identif$.tw.
49. detect$.tw.
50. diagnos$.tw.
51. (predictive adj4 value$).tw.
52. accura$.tw.
53. comparison.tw.
54. or/35–53
55. 27 and 11 and 4 and 54
56. 34 or 55
57. remove duplicates from 56
58. limit 57 to yr="1990 – 2009"
59. limit 58 to english language

Science Citation Index (1990 –14 March 2009), BIOSIS (1990 – 12 March 2009)

ISI Web of Knowledge:http://wok.mimas.ac.uk/

1 TS=(breast neoplasm* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc))
2 TS=(breast cancer* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc))
3 TS=(breast carcin* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc))
4 TS=(breast tumour* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc))
5 TS=(breast tumor* AND (recur* or secondary or contralateral or ipsilateral or ibtr or mcbc))
6 #1 or #2 or #3 or #4 or #5
7 #6 AND TS=mammogram*
8 #6 AND TS=mammograph*
9 #6 and TS=surveillance
10 #6 and TS=routine
11 #6 and TS=magnetic resonance imag*
12 #6 AND TS=mri
13 #6 and TS=ultrasound
14 #6 and TS=ultrasonograph*
15 #6 and TS=echo mammogra*
16 #6 and TS=echomammogra*
17 #6 and TS= (cliniCAL EXAM* OR SELF EXAM* OR PHYSICAL EXAM*)
18 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19 #18 AND TS=(sensitivity or specificity)
20 #18 AND TS=(ROC or receiver operat* characteristic)
21 #18 AND TS=(diagnos* or detect*)
22 #18 AND TS=(differentiat* or distinguish*)
23 #18 AND TS=(accura* or identif*)

# 24 #23 OR #22 OR #21 OR #20 OR #19 AND Language=(English) AND Document Type=(Article)
Databases=SCI-EXPANDED Timespan=1990–2009

Cochrane Library Issue 2, 2009 (Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews)

www3.interscience.wiley.com/

#1 MeSH descriptor Breast Neoplasms explode all trees
#2 (breast):ti
#3 (#1 OR #2)
#4 MeSH descriptor Neoplasm Recurrence, Local, this term only
#5 MeSH descriptor Neoplasms, Second Primary, this term only
#6 (recur* or second or secondary):ti,ab,kw or (contralateral or ipsilateral):ti,ab,kw or (ibtr or mcbc):ti,ab,kw
#7 (#4 OR #5 OR #6)
#8 MeSH descriptor Mammography explode all trees
#9 (mammograph* or mammogram*):ti,ab,kw
#10 MeSH descriptor Physical Examination, this term only
#11 MeSH descriptor Breast Self-Examination, this term only
#12 (physical NEAR/1 exam*):ti,ab,kw or (clinical NEAR/1 exam*):ti,ab,kw or (self NEAR/1 exam*):ti,ab,kw
#13 (surveillance):ti,ab,kw or (follow up):ti or (routine NEAR/3 visit*):ti,ab,kw or (routine NEAR/3 follow up):ab
#14 MeSH descriptor Magnetic Resonance Imaging, this term only
#15 MeSH descriptor Ultrasonography, Mammary, this term only
#16 (magnetic resonance imag* or mri):ti,ab,kw or (ultrasound or ultrasonograph*):ti,ab,kw or (echo mammogra* or echomammogra*):ti,ab,kw
#17 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 (#3 AND #7 AND #17)
#19 MeSH descriptor Neoplasm Recurrence, Local explode all trees with qualifier: DI
#20 MeSH descriptor Neoplasms, Second Primary explode all trees with qualifier: DI
#21 (#3 AND (#19 OR #20))
#22 #18 OR #21 (1990–2009)

CANCERLIT (20 March 2009)

The US National Library of Medicine: www.ncbi.nlm.nih.gov

#1 Search (breast neoplasms[majr] AND human[mh] AND english[la]) OR dcis[ti] OR lcis[ti] OR ((breast[ti] OR breasts[ti] OR mammary[ti] OR nipple[ti] OR nipples[ti]) AND ((cancer*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR malignan*[ti] OR tumor*[ti] OR tumour*[ti] OR neoplasm*[ti]) OR in situ[ti])) Limits: Cancer
#2 Search recur* or secondary or contralateral or ipsilateral or ibtr or mcbc Limits: Cancer
#3 Search #1 AND #2 Limits: Cancer
#4 Search ((((Magnetic resonance imaging[MeSH Terms]) OR (ultrasonography, mammary[MeSH Terms])) OR ("magnetic resonance imag* or mri"[Text Word])) OR ("ultrasound or ultrasonograph* or echo mammogra* or echomammogra*"[Text Word])) AND (#1 AND #2) Limits: English

Health Technology Assessment/Database of Abstracts of Reviews and Effects/NHS Economic Evaluation databases, March 2009

Centre for Reviews & Dissemination: http://nhscrd.york.ac.uk/welcome.htm

1 MeSH Breast Neoplasms EXPLODE 1 2

2 (recur* OR ipsilateral OR contralateral OR ibtr OR mcbc OR second OR secondary)
3 #1 and #2

MEDION, March 2009

www.mediondatabase.nl/

ICPC CODE=Female genital
AND Signssymp=Medical Imaging
AND Textword=breast

Clinical Trials, March 2009

http://clinicaltrials.gov/ct/gui/c/r

"Breast neoplasms"
AND
Mammography OR ultrasonography OR magnetic resonance imaging
AND
Recurrence or ipsilateral or ccontralateral or ibtr or mcbc

Current Controlled Trials, March 2009

www.controlled-trials.com/

Breast AND (mammography OR magnetic resonance imaging OR ultrasonography)

The World Health Organization International Clinical Trials Registry Platform, March 2009

World Health Organization: www.who.int/ictrp/en/

Breast AND (mammography OR magnetic resonance imaging OR ultrasonography)

National Research Register Archive

National Institute for Health Research portal: https://portal.nihr.ac.uk/Pages/NRRArchiveSearch.aspx

NIHR portfolio, March 2009

National Institute for Health Research portal: https://portal.nihr.ac.uk/Search/Advanced.aspx

Breast AND (mammography OR magnetic resonance imaging OR ultrasonography)

National Cancer Institute Clinical Trials, March 2009

The US National Institutes of Health: www.cancer.gov

breast cancer (female) AND mammography OR magnetic resonance imaging OR ultrasonography

Websites consulted

American College of Radiology
www.acr.org/

American Society of Breast Disease
www.asbd.org/

American Society of Clinical Oncology
www.asco.org/

Breast Cancer Surveillance Consortium
http://breastscreening.cancer.gov/

CancerWEB
www.infoventures.com/cancer/

Canadian Task Force on Preventive Health Care
www.ctfphc.org/

Cancer Research UK
www.cancerresearchuk.org/

European Society for Medical Oncology
www.esmo.org/

National Breast and Ovarian Cancer Centre
www.nbocc.org.au/

National Cancer Institute
www.cancer.gov/cancertopics/types/breast

National Comprehensive Cancer Network
www.nccn.org/index.asp

National Library for Health
www.library.nhs.uk/default.aspx

Royal College of Radiologists
www.rcr.ac.uk/

Surveillance, Epidemiology, and End Results (SEER) Program
http://seer.cancer.gov/

Appendix 18

Reports of included studies: systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

Belli 2003

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Boné 1995

Boné B, Aspelin P, Isberg B, Perbeck L, Veress B. Contrast-enhanced MR imaging of the breast in patients with breast implants after cancer surgery. *Acta Radiol* 1995;**36**:111–16.

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Kim 2009

Kim MJ, Kim EK, Kwak JY, Park BW, Kim SI, Sohn J, *et al.* Sonographic surveillance for the detection of contralateral metachronous breast cancer in an Asian population. *AJR Am J Roentgenol* 2009;**92**:221–8.

Mumtaz 1997

Mumtaz H, Davidson T, Hall-Craggs MA, Payley M, Walmsley K, Cowley G, *et al.* Comparison of magnetic resonance imaging and conventional triple assessment in locally recurrent breast cancer. *Br J Surg* 1997;**84**:1147–51.

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Viehweg P, Rotter K, Laniado M, Lampe D, Buchmann J, Kolbl H, *et al.* MR imaging of the contralateral breast in patients after breast-conserving therapy. *Eur Radiol* 2004;**14**:402–8.

Appendix 19

Reports of excluded studies: systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

Participants ineligible (n = 77)

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Crowe JP. The importance of preoperative breast MRI for patients newly diagnosed with breast cancer. *Breast J* 2009;**15**:52–60.

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Appendix 20

Data extraction form for the systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

HTA Mammography Surveillance

Diagnostic Accuracy (review 2) data extraction form

Version 4   May 2009

Study id: **Extractor initials:** **Date:**	

Study ids of linked reports:

Aim of study:

Types of participants:

□ Women without detectable metastatic disease who have received breast conserving surgery for primary breast cancer

□ Women without detectable metastatic disease who have received mastectomy for primary breast cancer

Test(s):

□ Mammography
□ GP follow up
□ Self examination
□ Self presentation (of symptoms)
□ MRI
□ Ultrasound
□ Hospital clinician led examination
□ Hospital nurse led examination

Outcomes reported:

□ IBTR

□ Test performance

□ *Adverse effects*
□ Radiological or other operator expertise
□ Interpretability/readability of tests
□ Acceptability of tests

□ MCBC

□ Test performance

□ *Adverse effects*
□ Radiological or other operator expertise
□ Interpretability/readability of tests
□ Acceptability of tests

Study design:

□ *RCT*
□ Non-randomised comparative study with some participants receiving the index test, some receiving the comparator test and all receiving the reference standard
□ *Direct head-to-head with all participants receiving index test, comparator test and reference standard*
□ *Cohort with all participants receiving either the index test or comparator and reference standard*

Multicentre study? □　*No* □　*Yes*　*If yes, number of centres:*

　　　Study start/end dates:　　　　　　　Duration of study:

　　　Country:

　　　Source of funding:

　　　Additional information on study design:

Inclusion criteria:

Exclusion criteria:

Characteristics of the participants

	Group 1	*Group 2*	*All*
Enrolled			
[For RCTs – number randomised]			
Received tests			
Received reference standard			
[Post randomisation exclusions]			

Analysed			
Lost to follow-up			

No Age: Mean
     Median
     SD
     Range
     No. <50
     No. 50 and over			

Menopausal status: No. premenopausal No. postmenopausal			
HRT Status: No. currently receiving HRT No. previously received HRT No. never received HRT			
Primary Treatment:			
No. received primary breast conserving surgery (WLE)			
No. received primary mastectomy			
No. reconstructed breast			
No. receiving treatment for primary breast cancer:			

Neoadjuvant radiotherapy			
Neoadjuvant chemotherapy			
Adjuvant radiotherapy			
Adjuvant chemotherapy			
Adjuvant tamoxifen /Endocrine			
Oopherectomy or ovarian ablation			

Additional patient information:

Characteristics of the tests

Index Test - Mammography

    Film   ☐

    Digital   ☐

Scoring system and positive test result defined as:

Details of interpreter/reader experience if reported:

Additional information on test (e.g. radiation dose, time taken, etc):

Comparator test:

- ☐   MRI
- ☐   Ultrasound

For the following comparators, a positive test result (e.g. lump identified by palpation) will initiate an imaging test prior to biopsy or Fine Needle Aspiration Cytology (FNAC). Please indicate whether a mammogram or other imaging test was conducted prior to biopsy/ FNAC for people with positive test results. Reported test performance (sensitivity/specificity) should reflect the comparator test and not the imaging test alone.

Mammo/Other prior to biopsy/FNAC

☐	GP follow up	☐
☐	Self Examination	☐
☐	Self presentation (of symptoms)	☐
☐	Hospital Clinician led examination	☐
☐	Hospital Nurse led examination	☐

Positive test result defined as:

Details of operator experience if reported:

Additional information on comparator test:

Reference standard:

Positive Index/Comparator test results verified by:

- ☐   Histopathological assessment of biopsied tissue
- ☐   Fine Needle Aspiration Cytology

Negative Index/Comparator test results verified by:

- ☐   Subsequent testing within a 3 year follow up period

Length of follow-up time for verifying negative index/comparator test results:

How was tumour size determined?

How was tumour grade determined?

Additional information on reference standard:

Results

IBTR/MCBC Tumour Type

Please record the number of women with IBTR and/or MCBC

No of women with: **No of women with:**

IBTR   MCBC

Please record the associated the number of women with the following for IBTR and/or MCBC:

IBTR – No of women with: **MCBC – No of women with:**

DCIS   DCIS

LCIS   LCIS

Invasive   Invasive

Grade 1   Grade 1

Grade 2   Grade 2

Grade 3   Grade 3

If reported, please record the number of women with the following:

IBTR   MCBC

<u>Size</u>   <u>Size</u>

Not measurable

Invasive tumor in mm
(largest dimension of
dominant invasive
tumour focus)

Whole size of tumor
(invasive plus
surrounding DCIS if DCIS
extends > 1 mm beyond
invasive)

<u>Morphologic type</u>
a. Ductal/no specific (ductal NST)

b. Lobular

c. Other

Test performance *(true and false positives and negatives)*
Record data for each level of analysis e.g. patient, all biopsies, e.g. Size, grade, DCIS, Invasive, etc on separate sheet(s) containing 2x2 tables

General information on IBTR/MCBC:

Adverse events associated with tests
General information on adverse events:

Adverse events reported	*Group 1* no. of women with event and % of total women in group	*Group 2* no. of women with event and % of total women in group	*All* no. of women with event and % of total women in study

Inter-observer agreement			
Scale used e.g. Kappa			*Notes*
Additional study information:			
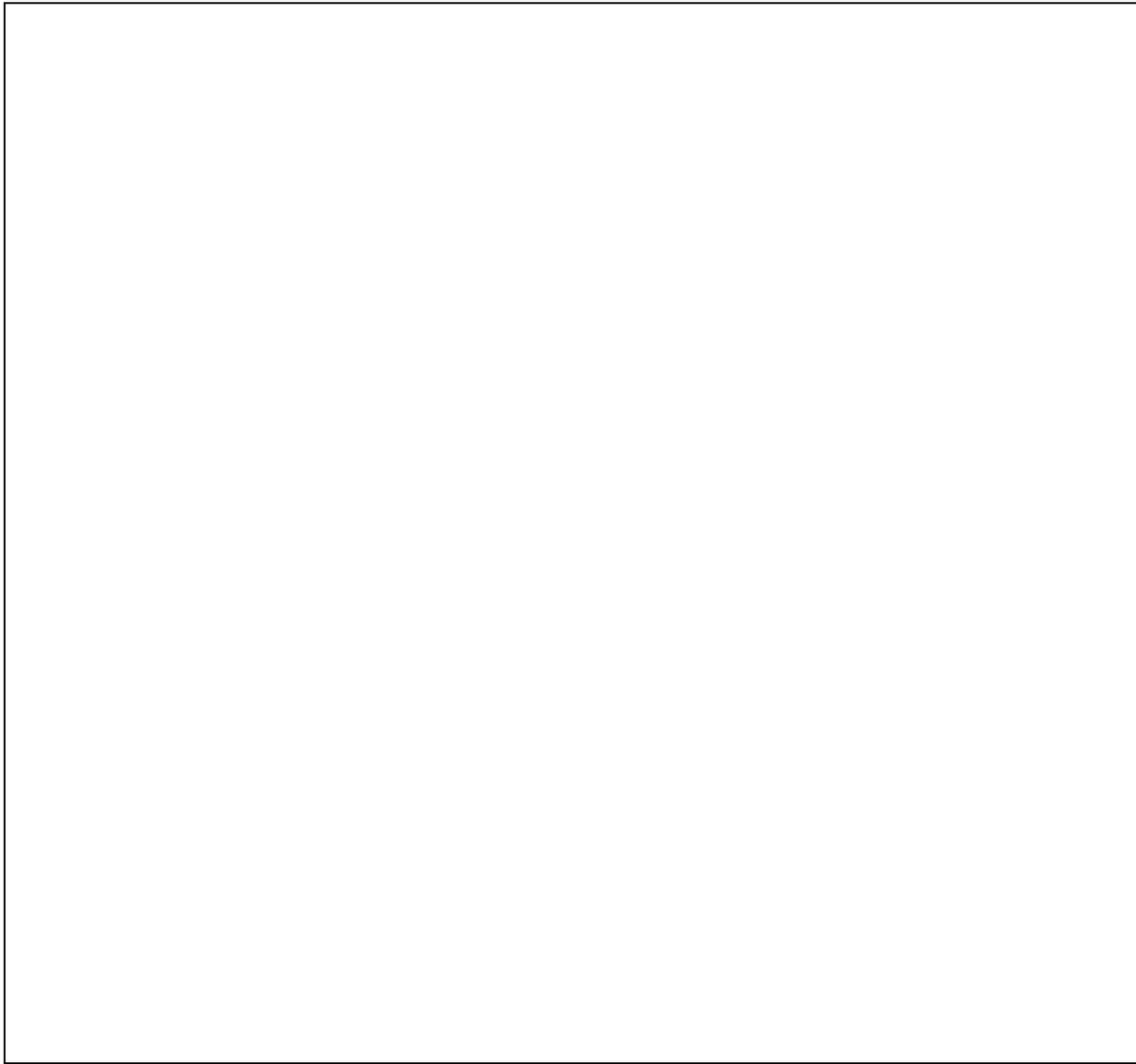
HTA Mammography Surveillance- Diagnostic Accuracy (review 2) 2x2 form

Version 2, March 2009

Study id: **Extractor initials:**   **Date:**

Study ids of linked reports:

Please record the unit of analysis as reported by the study authors – e.g. women level, biopsy level. If given, please record unit of analysis by our considered sub-groups: Age, menopausal status, HRT status, primary treatment, second tumour type.

Test: IBTR/MCBC

	Unit of analysis:		
	With disease	**Without disease**	
Positive test	TP	FP	**Total testing positive**
Negative test	FN	TN	**Total testing negative**
	Total with disease	**Total without disease**	

Sensitivity:

Specificity:

Test: IBTR/MCBC

	Unit of analysis:		
	With disease	**Without disease**	
Positive test	TP	FP	**Total testing positive**
Negative test	FN	TN	**Total testing negative**
	Total with disease	**Total without disease**	

Sensitivity:

Specificity:

Appendix 21

Quality assessment tool used in the systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

HTA Mammography Surveillance – Diagnostic Accuracy review 2

Quality Assessment Form

Version 4   **May 2010**

Study id: Extractor initials: Date:

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice? (women previously treated for primary breast cancer)			
2.	Is the reference standard likely to correctly classify the target condition?			
3a	For positive test results, is the time period between reference standard and index/comparator test short enough to be reasonably sure that the target condition did not change between the two tests? (biopsy or FNAC within 3 months, histopathology within 6 months)			
3b	For negative test results, is the time period between the index/comparator test and the reference standard short enough to be reasonably sure that the target condition did not change between the two tests? (follow-up within 3 years)			
4.	Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?			
5a	Did patients testing positively on the index/comparator test receive the same reference standard (i.e. FNAC or biopsy)?			
5b	Did patients testing negatively on the index/comparator test receive the same reference standard (i.e. follow up)?			
6.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
7.	Were the index test results interpreted without knowledge of the results of the reference standard?			
8.	Were the reference standard results interpreted without knowledge of the results of the index test?			
9.	Were index and comparator tests interpreted independently (if no record the sequence)?			
10.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?			
11.	Were uninterpretable/intermediate test results reported?			
12.	Were withdrawals from the study explained?			

Adapted from the QUADAS Tool. Whiting et al. BMC Medical Research Methodology 2003 3:25 doi:10.1186/1471-2288-3-25

Appendix 22

Characteristics of the included studies for the systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

Study ID	Study design	Index tests	Comparator test	Test purpose
Belli 2002[66] *Time period*: NR *Country*: Italy *Study design*: direct head-to-head cohort	*Enrolled*: 23 *Analysed*: 23 *BCT*: 23 *Mastectomy*: 0 *Age (years)*: mean 52.9 years; median NR; SD, 10.8; range 35–75 years	*Index test*: MRI for local recurrence	XRM, CE, US for local recurrence	Surveillance for detecting IBTR
Boné 1995[64] *Time period*: September 1992 to September 1993 *Country*: Sweden *Study design*: direct head-to-head cohort	*Enrolled*: 83 *Analysed*: 83 *BCT*: 0 *Mastectomy*: 83, all with breast reconstruction and implants *Age (years)*: mean NR; median 50 years; SD, NR; range 33–75 years	*Index test*: XRM for local and contralateral recurrence	MRI, CE for local and contralateral recurrence	Surveillance for detecting IBTR and MCBC
Drew 1998[67] *Time period*: NR *Country*: UK *Study design*: direct head-to-head cohort	*Enrolled*: 105 *Analysed*: 105 *BCT*: 105 *Mastectomy*: 0 *Age (years)*: mean NR; median 58 years; SD, NR; range 50–65 years	*Index test*: MRI for local recurrence	XRM, CE, XRM + CE for local recurrence	Surveillance for detecting IBTR
Kim 2009[65] *Time period*: January 2003 to December 2003 *Country*: South Korea *Study design*: direct head-to-head cohort	*Enrolled*: 1431 *Analysed*: 1256 *BCT*: 292 *Mastectomy*: 964 *Age (years)*: mean 50 years; median 49 years; SD, 10 years; range 22–82 years	*Index test*: adjunct US (XRM + US) for contralateral recurrence	None	Surveillance for detecting MCBC

Study ID	Study design	Index tests	Comparator test	Test purpose
Mumtaz 1997[68] *Time period*: NR *Country*: UK *Study design*: direct head-to-head cohort	*Enrolled*: 30 *Analysed*: 30 *BCT*: 30 *Mastectomy*: 0 *Age (years)*: recurrence patients mean NR; median 52 years; SD, NR; range 34–80 years; recurrence-free patients mean NR; median 62 years; SD, NR; range 47–79 years	*Index test*: XRM for local recurrence	MRI for local recurrence	Confirmation of suspicious result on prior diagnostic test (previous clinical suspicion)
Rieber 1997[69] *Time period*: NR *Country*: Germany *Study design*: cohort	*Enrolled*: 140 *Analysed*: 140 *BCT*: 140 *Mastectomy*: 0 *Age (years)*: mean 52.8 years; median NR; SD, NR; range 32–81 years	*Index test*: MRI for local recurrence	None	Confirmation of suspicious result on prior diagnostic test (suspicious finding on at least one of the following: clinical examination, ultrasound or mammography)
Shin 2005[71] *Time period*: January 2001 to February 2004 *Country*: South Korea *Study design*: cohort	*Enrolled*: 1968 *Analysed*: 1968 *BCT*: NR *Mastectomy*: NR *Age (years)*: mean 49 years; median NR; SD, NR; range 32–69 years	*Index test*: US for local and contralateral recurrence	None	Surveillance for detecting IBTR and MCBC
Ternier 2006[72] *Time period*: May 1997 to May 2002 *Country*: France *Study design*: direct head-to-head cohort	*Enrolled*: 103 *Analysed*: 103 *BCT*: 103 *Mastectomy*: 0 *Age (years)*: mean NR; median 60 years; SD, NR; range 32–82 years	*Index test*:[a] XRM for local recurrence	CE, US for local recurrence	Confirmation of suspicious result on prior diagnostic test (suspicious finding on at least one of the following: clinical examination, ultrasound or mammography)
Viehweg 2004[70] *Time period*: August 1994 to April 2001 *Country*: Germany *Study design*: direct head-to-head cohort	*Enrolled*: 119 *Analysed*: 119 *BCT*: 119 *Mastectomy*: 0 *Age (years)*: mean NR; median 55.7 years; SD, 9.8; range 25–78 years	*Index test*: MRI for contralateral recurrence	CM (XRM + CE + US); MRI + CM for contralateral recurrence	Surveillance for detecting MCBC

CE, clinical examination; CM, conventional methods; US, ultrasound; XRM, X-ray mammography.

a Study authors considered computerised tomography as the index test in this study but this test was not considered as an included comparator in this review.

Appendix 23

Quality assessment of individual studies included in the systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

TABLE 58 Quality assessment for included studies of routine surveillance tests

Study ID	Q1	Q2	Q3a	Q3b	Q4	Q5a	Q5b	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Boné 1995[64]	-	+	?	+	+	+	+	+	+	?	?	+	+	+
Drew 1998[67]	+	+	?	+	-	+	+	+	+	?	+	+	+	+
Viehweg 2004[70]	+	+	?	+	+	+	+	+	?	?	-	+	-	+
Shin 2005[71]	+	+	+	+	?	+	?	+	+	?	-	+	+	+
Kim 2009[65]	+	+	?	+	+	+	+	+	+	?	-	+	?	+

NA, not applicable; +, yes to the question; −, no to the question; ?, unclear.

TABLE 59 Quality assessment for included studies of non-routine surveillance tests

Study ID	Q1	Q2	Q3a	Q3b	Q4	Q5a	Q5b	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Mumtaz 1997[68]	+	+	?	+	+	+	+	+	+	?	+	+	+	+
Rieber 1997[69]	+	+	?	+	+	+	+	+	+	?	-	?	+	+
Belli 2002[66]	+	+	?	+	+	+	+	+	+	?	+	+	?	?
Ternier 2006[72]	+	+	?	+	+	+	+	+	+	?	-	+	+	+

NA, not applicable; +, yes to the question; −, no to the question; ?, unclear.

Appendix 24

Histology of cancers detected and not detected (true-positives and false-negatives): systematic review of test performance of surveillance mammography and comparator tests in detecting IBTR/MCBC

TABLE 60 Histology of true-positive and false-negative test results for surveillance mammography

Test	Study ID	True-positives	False-negatives
Surveillance mammography	Boné 1995[64]	DCIS $n=7$ ILC $n=1$ IDC $n=2$	IDC $n=4$ ILC $n=1$
	Mumtaz 1997[68]		*Mammographic findings*: deformed dense breast $n=4$; scarring and benign linear microcalcifications $n=3$
	Viehweg 2004[70]	*Minimally invasive carcinoma plus*: DCIS grade 1 non-comedo $n=1$ DCIS grade 1 comedo $n=1$ IDC grade 2 $n=2$ DCIS grade 2 non-comedo $n=1$ Ductolobular carcinoma plus DCIS grade 2 non-comedo $n=1$	Minimally invasive carcinoma plus DCIS grade 3 comedo $n=1$ DCIS grade 1 non-comedo $n=1$ DCIS grade 2 non-comedo $n=3$ IDC grade 2 $n=1$
	Kim 2009[65]	IDC $n=12$ ILC $n=1$ DCIS $n=3$	DCIS $n=2$

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

TABLE 61 Histology of true-positive and false-negative test results for ultrasound

Test	Study ID	True-positives	False-negatives
Ultrasound	Kim 2009[65]	IDC $n=12$ ILC $n=1$ DCIS $n=2$	IDC $n=1$ DCIS $n=2$
	Shin 2005[71]	Most frequently lymphadenopathy (non-palpable?)	
	Viehweg 2004[70]	DCIS grade 2 non-comedo $n=1$ Ductolobular carcinoma plus DCIS grade 2 non-comedo $n=1$	Minimally invasive carcinoma plus DCIS grade 1 non-comedo $n=1$ Minimally invasive carcinoma plus DCIS grade 3 comedo $n=1$ DCIS grade 1 non-comedo $n=1$ DCIS grade 2 non-comedo $n=2$ DCIS grade 1 comedo $n=1$ IDC grade 2 $n=3$

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

TABLE 62 Histology of true-positive and false-negative test results for MRI

Test	Study ID	True-positives	False-negatives
MRI	Boné 1995[64]	IDC $n=5$ DCIS $n=5$ ILC $n=2$	DCIS, $n=1$ IDC, $n=1$
	Mumtaz 1997[68]		Diffuse scattered cancer cells within a dense fibrotic stroma with no discrete tumour focus $n=1$
	Viehweg 2004[70]	Minimally invasive carcinoma plus DCIS grade 1 non-comedo $n=1$	DCIS grade 1 non-comedo $n=1$
		Minimally invasive carcinoma plus DCIS grade 3 comedo $n=1$	
		DCIS grade 2 non-comedo $n=2$	
		Minimally invasive carcinoma plus DCIS grade 1:	
		comedo $n=1$	
		IDC grade 2 $n=3$	

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

TABLE 63 Histology of true-positive and false-negative test results for clinical examination

Test	Study ID	True-positives	False-negatives
CE	Boné 1995[64]	ILC $n=2$ IDC $n=4$ DCIS $n=1$	IDC $n=2$ DCIS $n=5$
	Viehweg 2004[70]	IDC grade 2 $n=1$ Ductolobular carcinoma plus DCIS grade 2 non-comedo $n=1$	Minimally invasive carcinoma plus DCIS grade 1 non-comedo $n=1$ Minimally invasive carcinoma plus DCIS grade 3 comedo $n=1$ DCIS grade 1 non-comedo $n=1$ DCIS grade 2 non-comedo $n=2$ Minimally invasive carcinoma plus DCIS grade 1: comedo $n=1$ IDC grade 2 $n=2$
	Kim 2009[65]	IDC $n=5$	IDC $n=8$ ILC $n=1$ DCIS $n=4$

CE, clinical examination; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

Appendix 25

Univariate Cox regression models for the WMCIU cohorts

TABLE 64 Cox proportional hazards regression models for time to IBTR in BCS cohort

	n	*N*	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤ 34	26	350	7.4	3.27	2.17 to 4.92	< 0.001	2.28	1.51 to 3.47	< 0.001
35–49	138	3513	3.9	1.80	1.45 to 2.24	< 0.001	1.44	1.15 to 1.80	0.002
50–64	189	8511	2.2	(1.00)			(1.00)		
65–74	54	3491	1.5	0.80	0.59 to 1.09	0.154	0.72	0.53 to 0.97	0.033
75–79	25	1034	2.4	1.25	0.83 to 1.89	0.284	0.96	0.63 to 1.47	0.852
80+	23	807	2.9	1.93	1.27 to 2.93	0.002	1.28	0.81 to 2.03	0.289
Grade									
1	60	4193	1.4	(1.00)			(1.00)		
2	175	7697	2.3	1.75	1.31 to 2.35	< 0.001	1.53	1.14 to 2.07	0.005
3	204	5388	3.8	3.15	2.36 to 4.21	< 0.001	2.32	1.71 to 3.16	< 0.001
Unknown	16	428	3.7	2.75	1.69 to 4.49	< 0.001	1.85	1.06 to 3.26	0.032
Size (mm)									
≤ 10	68	3473	2.0	(1.00)			(1.00)		
> 10 to < 20	173	8663	2.0	1.02	0.77 to 1.35	0.892	0.81	0.61 to 1.09	0.161
≥ 20	179	4885	3.7	2.11	1.60 to 2.80	< 0.001	1.31	0.97 to 1.78	0.078
Size cat. unknown	35	685	5.1	2.23	1.51 to 3.30	< 0.001	1.28	0.83 to 1.96	0.268
Nodes									
0	231	11,630	2.0	(1.00)			(1.00)		
1–3	103	3367	3.1	1.64	1.30 to 2.07	< 0.001	1.33	1.04 to 1.69	0.021
4+	59	1232	4.8	2.98	2.23 to 3.96	< 0.001	2.04	1.51 to 2.77	< 0.001
Unknown	62	1477	4.2	2.14	1.63 to 2.80	< 0.001	2.06	1.51 to 2.81	< 0.001
Vascular invasion									
No	277	12,887	2.1	(1.00)			(1.00)		
Yes	140	3559	3.9	1.96	1.60 to 2.40	< 0.001	1.26	1.01 to 1.57	0.043
Unknown	38	1260	3.0	1.40	1.02 to 1.93	0.040	0.98	0.68 to 1.41	0.928

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 65 Cox proportional hazards regression models for time to MCBC occurrence in BCS cohort

	n	N	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	p-value	HR	95% CI	p-value
Age (years)									
≤34	11	350	3.1	1.62	0.88 to 2.98	0.124	1.54	0.82 to 2.86	0.177
35–49	55	3513	1.6	0.87	0.64 to 1.19	0.390	0.85	0.62 to 1.16	0.294
50–64	150	8511	1.8	(1.00)					
65–74	33	3491	0.9	0.62	0.43 to 0.90	0.012	0.61	0.42 to 0.89	0.010
75–79	6	1034	0.6	0.36	0.16 to 0.81	0.014	0.34	0.15 to 0.77	0.010
80+	5	807	0.6	0.49	0.20 to 1.19	0.116	0.46	0.18 to 1.14	0.093
Grade									
1	69	4193	1.6	(1.00)			(1.00)		
2	102	7697	1.3	0.91	0.67 to 1.24	0.558	0.92	0.68 to 1.26	0.623
3	79	5388	1.5	1.11	0.81 to 1.53	0.524	1.06	0.75 to 1.49	0.756
Unknown	10	428	2.3	1.27	0.69 to 2.35	0.439	1.40	0.71 to 2.76	0.329
Size (mm)									
≤10	45	3473	1.3	(1.00)			(1.00)		
>10 to <20	125	8663	1.4	1.13	0.80 to 1.59	0.485	1.25	0.88 to 1.76	0.217
≥20	74	4885	1.5	1.35	0.93 to 1.96	0.109	1.60	1.08 to 2.38	0.019
Size cat. unknown	16	685	2.3	1.54	0.90 to 2.63	0.115	1.81	1.01 to 3.22	0.044
Nodes									
0	183	11,630	1.6	(1.00)			(1.00)		
1–3	38	3367	1.1	0.75	0.53 to 1.06	0.100	0.72	0.50 to 1.03	0.075
4+	19	1232	1.5	1.19	0.74 to 1.91	0.473	1.20	0.73 to 1.96	0.479
Unknown	20	1477	1.4	0.89	0.58 to 1.38	0.608	1.07	0.67 to 1.73	0.771
Vascular invasion									
No	204	12,887	1.6	(1.00)			(1.00)		
Yes	43	3559	1.2	0.80	0.57 to 1.11	0.175	0.74	0.52 to 1.05	0.096
Unknown	13	1260	1.0	0.68	0.41 to 1.13	0.139	0.58	0.33 to 1.01	0.053

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 66 Cox proportional hazards regression models for time to all-cause death in BCS cohort

	n	N	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤34	60	350	17.1	1.57	1.21 to 2.04	0.001	1.00	0.77 to 1.30	0.987
35–49	371	3513	10.6	1.05	0.93 to 1.18	0.463	0.78	0.69 to 0.89	<0.001
50–64	848	8511	10.0	(1.00)			(1.00)		
65–74	594	3491	17.0	1.96	1.76 to 2.17	<0.001	1.80	1.62 to 2.01	<0.001
75–79	293	1034	28.3	3.16	2.77 to 3.61	<0.001	2.55	2.23 to 2.93	<0.001
80+	362	807	44.9	6.49	5.74 to 7.33	<0.001	4.83	4.22 to 5.52	<0.001
Grade									
1	344	4193	8.2	(1.00)			(1.00)		
2	1002	7697	13.0	1.77	1.57 to 2.00	<0.001	1.33	1.17 to 1.50	<0.001
3	1114	5388	20.7	3.04	2.69 to 3.43	<0.001	2.20	1.93 to 2.50	<0.001
Unknown	68	428	15.9	2.05	1.64 to 2.57	<0.001	1.15	0.88 to 1.50	0.207
Size (mm)									
≤10	230	3473	6.6	(1.00)			(1.00)		
>10 to <20	1030	8663	11.9	1.81	1.57 to 2.09	<0.001	1.32	1.14 to 1.53	<0.001
≥20	1117	4885	22.9	3.92	3.40 to 4.52	<0.001	2.04	1.76 to 2.37	<0.001
Size cat. unknown	151	685	22.0	2.83	2.33 to 3.45	<0.001	1.54	1.25 to 1.91	<0.001
Nodes									
0	1073	11,630	9.2	(1.00)			(1.00)		
1–3	573	3367	17.0	1.94	1.75 to 2.15	<0.001	1.57	1.41 to 1.74	<0.001
4+	416	1232	33.8	4.44	3.96 to 4.97	<0.001	2.96	2.62 to 3.34	<0.001
Unknown	466	1477	31.6	3.27	2.94 to 3.63	<0.001	1.92	1.70 to 2.17	<0.001
Vascular invasion									
No	1460	12,887	11.3	(1.00)			(1.00)		
Yes	847	3559	23.8	2.22	2.04 to 2.41	<0.001	1.36	1.24 to 1.49	<0.001
Unknown	221	1260	17.5	1.50	1.31 to 1.71	<0.001	1.15	0.99 to 1.33	0.066
Ipsilateral recurrence									
No	2350	17,251	13.6	(1.00)			(1.00)		
Yes	178	455	39.1	2.29	1.97 to 2.67	<0.001	1.76	1.51 to 2.05	<0.001
Contralateral occurrence									
No	2475	17,446	14.2	(1.00)			(1.00)		
Yes	53	260	20.4	0.99	0.76 to 1.30	0.97	1.05	0.80 to 1.39	0.715

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 67 Cox proportional hazards regression models for time to death from breast cancer in BCS cohort

	n	N	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤ 34	55	350	15.7	2.33	1.77 to 3.08	< 0.001	1.21	0.91 to 1.60	0.182
35–49	310	3513	8.8	1.39	1.21 to 1.60	< 0.001	0.90	0.78 to 1.04	0.157
50–64	535	8511	6.3	(1.00)			(1.00)		
65–74	278	3491	8.0	1.43	1.24 to 1.65	< 0.001	1.28	1.10 to 1.48	0.001
75–79	96	1034	9.3	1.63	1.32 to 2.03	< 0.001	1.27	1.02 to 1.58	0.034
80+	104	807	12.9	2.85	2.32 to 3.51	< 0.001	2.06	1.65 to 2.57	< 0.001
Grade									
1	76	4193	1.8	(1.00)			(1.00)		
2	489	7697	6.4	3.87	3.04 to 4.92	< 0.001	2.60	2.03 to 3.32	< 0.001
3	786	5388	14.6	9.56	7.55 to 12.10	< 0.001	5.31	4.17 to 6.77	< 0.001
Unknown	27	428	6.3	4.21	2.90 to 6.12	< 0.001	2.39	1.62 to 3.54	0.207
Size (mm)									
≤ 10	75	3473	2.2	(1.00)			(1.00)		
> 10 to < 20	510	8663	5.9	2.75	2.16 to 3.50	< 0.001	1.73	1.35 to 2.21	< 0.001
≥ 20	717	4885	14.7	7.66	6.04 to 9.71	< 0.001	3.04	2.37 to 3.89	< 0.001
Size cat. unknown	76	685	11.1	4.61	3.39 to 6.25	< 0.001	2.09	1.52 to 2.88	< 0.001
Nodes									
0	505	11,630	4.3	(1.00)			(1.00)		
1–3	366	3367	10.9	2.63	2.30 to 3.01	< 0.001	1.82	1.59 to 2.10	< 0.001
4+	332	1232	26.9	7.42	6.46 to 8.53	< 0.001	3.88	3.34 to 4.51	< 0.001
Unknown	175	1477	11.8	2.72	2.30 to 3.22	< 0.001	2.23	1.85 to 2.69	< 0.001
Vascular invasion									
No	679	12,887	5.3	(1.00)			(1.00)		
Yes	606	3559	17.0	3.40	3.04 to 3.79	< 0.001	1.59	1.41 to 1.79	< 0.001
Unknown	93	1260	7.4	1.44	1.17 to 1.76	< 0.001	1.09	0.88 to 1.36	0.430
Ipsilateral recurrence									
No	1247	17,251	7.2						
Yes	131	455	28.8	3.30	2.76 to 3.94	< 0.001	2.13	1.78 to 2.56	< 0.001
Contralateral occurrence									
No	1375	17,446	7.9	(1.00)					
Yes	3	260	1.2	1.13	0.86 to 1.49	0.378			

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 68 Multiple Cox proportional hazards regression models for time to IBTR in mastectomy cohort

	n	N	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤34	10	360	2.8	1.36	0.71 to 2.60	0.352	0.97	0.51 to 1.87	0.937
35–49	65	3188	2.0	0.97	0.72 to 1.32	0.854	0.85	0.62 to 1.16	0.298
50–64	110	5229	2.1	(1.00)			(1.00)		
65–74	77	3422	2.3	1.11	0.83 to 1.48	0.498	1.14	0.85 to 1.54	0.368
75–79	26	1547	1.7	0.90	0.59 to 1.38	0.629	0.97	0.63 to 1.49	0.882
80+	22	1425	1.5	1.05	0.67 to 1.63	0.834	0.98	0.62 to 1.57	0.945
Grade									
1	23	1827	1.3	(1.00)			(1.00)		
2	116	6918	1.7	1.48	0.95 to 2.32	0.085	1.23	0.78 to 1.94	0.363
3	157	5852	2.7	2.78	1.79 to 4.31	<0.001	2.06	1.31 to 3.24	0.002
Unknown	14	574	2.4	2.34	1.28 to 4.30	0.006	1.44	0.73 to 2.82	0.293
Size (mm)									
≤10	13	1103	1.2	(1.00)			(1.00)		
>10 to <20	68	4224	1.6	1.38	0.76 to 2.51	0.283	1.24	0.68 to 2.25	0.485
≥20	175	8627	2.0	2.04	1.16 to 3.59	0.013	1.43	0.80 to 2.56	0.224
Size cat. unknown	54	1217	4.4	3.82	2.09 to 6.97	<0.001	2.61	1.40 to 4.84	0.002
Nodes									
0	114	6938	1.6	(1.00)			(1.00)		
1–3	68	4147	1.6	1.10	0.82 to 1.49	0.518	0.95	0.69 to 1.29	0.723
4+	97	3402	2.9	2.33	1.78 to 3.06	<0.001	1.62	1.20 to 2.19	0.002
Unknown	31	684	4.5	3.42	2.35 to 4.98	<0.001	2.55	1.65 to 3.95	<0.001
Vascular invasion									
No	126	8608	1.5	(1.00)			(1.00)		
Yes	150	5341	2.8	2.24	1.76 to 2.84	<0.001	1.68	1.29 to 2.19	<0.001
Unknown	34	1222	2.8	2.14	1.49 to 3.06	<0.001	1.25	0.82 to 1.90	0.307

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 69 Multiple Cox proportional hazards regression models for time to MCBC occurrence in mastectomy cohort

	n	N	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤ 34	13	360	3.6	1.79	1.01 to 3.17	0.048	1.55	0.87 to 2.77	0.138
35–49	64	3188	2.0	0.96	0.71 to 1.31	0.817	0.89	0.65 to 1.21	0.459
50–64	114	5229	2.2	(1.00)			(1.00)		
65–74	52	3422	1.5	0.79	0.57 to 1.09	0.156	0.77	0.55 to 1.07	0.118
75–79	13	1547	0.8	0.45	0.25 to 0.80	0.007	0.45	0.25 to 0.81	0.007
80+	6	1425	0.4	0.31	0.15 to 0.68	0.003	0.27	0.12 to 0.61	0.002
Grade									
1	31	1827	1.7	(1.00)			(1.00)		
2	110	6918	1.6	1.03	0.69 to 1.54	0.870	0.91	0.61 to 1.37	0.660
3	111	5852	1.9	1.52	1.02 to 2.26	0.040	1.18	0.78 to 1.79	0.436
Unknown	10	574	1.7	1.12	0.57 to 2.18	0.742	0.87	0.41 to 1.86	0.726
Size (mm)									
≤ 10	14	1103	1.3	(1.00)			(1.00)		
> 10 to < 20	67	4224	1.6	1.42	0.77 to 2.63	0.263	1.45	0.78 to 2.69	0.244
≥ 20	156	8627	1.8	1.96	1.09 to 3.53	0.025	1.81	0.99 to 3.31	0.054
Size cat. unknown	25	1217	2.1	2.01	1.03 to 3.94	0.042	1.74	0.87 to 3.50	0.117
Nodes									
0	110	6938	1.6	(1.00)			(1.00)		
1–3	64	4147	1.5	1.08	0.79 to 1.47	0.634	0.95	0.69 to 1.31	0.774
4+	75	3402	2.2	1.90	1.42 to 2.55	< 0.001	1.53	1.10 to 2.12	0.012
Unknown	13	684	1.9	1.40	0.81 to 2.45	0.231	1.44	0.76 to 2.75	0.264
Vascular invasion									
No	137	8608	1.6	(1.00)			(1.00)		
Yes	105	5341	2.0	1.44	1.12 to 1.86	0.005	1.09	0.82 to 1.45	0.543
Unknown	20	1222	1.6	1.07	0.67 to 1.69	0.784	0.89	0.53 to 1.50	0.669

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 70 Multiple Cox proportional hazards regression models for time to death from all causes in mastectomy cohort

	n	N	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤34	108	360	30.0	1.37	1.13 to 1.67	0.002	0.99	0.81 to 1.20	0.895
35–49	647	3188	20.3	0.91	0.82 to 1.00	0.042	0.78	0.71 to 0.86	<0.001
50–64	1179	5229	22.5	(1.00)			(1.00)		
65–74	1088	3422	31.8	1.51	1.39 to 1.64	<0.001	1.54	1.42 to 1.68	<0.001
75–79	608	1547	39.3	2.06	1.86 to 2.27	<0.001	2.18	1.98 to 2.41	<0.001
80+	715	1425	50.2	3.14	2.87 to 3.45	<0.001	3.29	2.99 to 3.61	<0.001
Grade									
1	336	1827	18.4	(1.00)			(1.00)		
2	1697	6918	24.5	1.50	1.34 to 1.69	<0.001	1.21	1.08 to 1.36	0.001
3	2148	5852	36.7	2.68	2.39 to 3.01	<0.001	2.02	1.79 to 2.27	<0.001
Unknown	164	574	28.6	1.85	1.56 to 2.19	<0.001	1.35	1.13 to 1.61	0.001
Size (mm)									
≤10	125	1103	11.3	(1.00)			(1.00)		
>10 to <20	846	4224	20.0	1.79	1.48 to 2.15	<0.001	1.38	1.14 to 1.66	0.001
≥20	2926	8627	33.9	3.60	3.01 to 4.31	<0.001	2.02	1.68 to 2.42	<0.001
Size cat. unknown	448	1217	36.8	3.39	2.78 to 4.12	<0.001	2.10	1.72 to 2.56	<0.001
Nodes									
0	1286	6938	18.5	(1.00)			(1.00)		
1–3	1115	4147	26.9	1.61	1.49 to 1.75	<0.001	1.50	1.38 to 1.63	<0.001
4+	1589	3402	46.7	3.45	3.20 to 3.71	<0.001	2.70	2.49 to 2.92	<0.001
Unknown	355	684	51.9	3.42	3.06 to 3.82	<0.001	2.45	2.16 to 2.77	<0.001
Vascular invasion									
No	1866	8608	21.7	(1.00)			(1.00)		
Yes	2079	5341	38.9	2.09	1.96 to 2.23	<0.001	1.37	1.28 to 1.47	<0.001
Unknown	400	1222	32.7	1.67	1.51 to 1.85	<0.001	1.14	1.01 to 1.28	0.030
Ipsilateral recurrence									
No	4150	14,861	27.9						
Yes	195	310	62.9	2.14	1.86 to 2.47	<0.001	1.64	1.42 to 1.89	<0.001
Contralateral occurrence									
No	4245	14,909	28.5						
Yes	100	262	38.2	1.01	0.83 to 1.24	0.901	0.99	0.81 to 1.21	0.906

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 71 Multiple Cox proportional hazards regression models for time to death from breast cancer in mastectomy cohort

	n	*N*	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤ 34	96	360	26.7	1.61	1.30 to 1.98	< 0.001	1.08	0.87 to 1.33	0.477
35–49	562	3188	17.6	1.03	0.93 to 1.15	0.561	0.85	0.76 to 0.94	0.002
50–64	901	5229	17.2	(1.00)			(1.00)		
65–74	632	3422	18.5	1.14	1.03 to 1.27	0.009	1.17	1.06 to 1.30	0.002
75–79	269	1547	17.4	1.17	1.03 to 1.34	0.020	1.26	1.10 to 1.44	0.002
80+	253	1425	17.8	1.39	1.21 to 1.60	< 0.001	1.51	1.31 to 1.74	0.001
Grade									
1	117	1827	6.4	(1.00)			(1.00)		
2	924	6918	13.4	2.32	1.91 to 2.81	< 0.001	1.68	1.38 to 2.04	< 0.001
3	1585	5852	27.1	5.55	4.60 to 6.70	< 0.001	3.38	2.79 to 4.10	< 0.001
Unknown	87	574	15.2	2.98	2.32 to 3.84	< 0.001	1.90	1.43 to 2.51	< 0.001
Size (mm)									
≤ 10	49	1103	4.4	(1.00)			(1.00)		
> 10 to < 20	438	4224	10.4	2.36	1.75 to 3.17	< 0.001	1.74	1.29 to 2.34	< 0.001
≥ 20	1916	8627	22.2	5.93	4.46 to 7.87	< 0.001	2.83	2.12 to 3.77	< 0.001
Size cat. unknown	310	1217	25.5	6.00	4.45 to 8.09	< 0.001	3.08	2.27 to 4.18	< 0.001
Nodes									
0	568	6938	8.2	(1.00)			(1.00)		
1–3	714	4147	17.2	2.32	2.07 to 2.59	< 0.001	1.92	1.71 to 2.15	< 0.001
4+	1250	3402	36.7	5.99	5.42 to 6.62	< 0.001	3.89	3.49 to 4.34	< 0.001
Unknown	181	684	26.5	4.07	3.48 to 4.76	< 0.001	2.96	2.47 to 3.54	< 0.001
Vascular invasion									
No	942	8608	10.9	(1.00)			(1.00)		
Yes	1533	5341	28.7	3.02	2.79 to 3.28	< 0.001	1.51	1.38 to 1.65	< 0.001
Unknown	238	1222	19.5	2.00	1.75 to 2.29	< 0.001	1.28	1.10 to 1.49	0.002
Ipsilateral recurrence									
No	2558	14,861	17.2						
Yes	155	310	50.0	2.78	2.37 to 3.27	< 0.001	2.12	1.80 to 2.50	< 0.001
Contralateral occurrence									
No	2707	14,909	18.2						
Yes	6	262	2.3	0.09	0.04 to 0.19	< 0.001			

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

Appendix 26

Univariate Cox regression models for the Edinburgh cohort

TABLE 72 Description of the Edinburgh breast cancer cohort

	n = 1439	
Age at diagnosis (years)		
Mean (SD)	56 (11)	
Median (25th, 75th centile)	56 (50, 63)	
Minimum, maximum	24, 91	
	n	***%***
Age categories (years)		
≤ 34	40	2.8
35–49	308	21.4
50–64	826	57.4
65–74	201	14.0
75+	64	4.4
Grade		
1	363	25.2
2	642	44.6
3	402	27.9
Unknown	32	2.2
Size (mm)		
≤ 10	339	23.6
> 10 to < 20	632	43.9
≥ 20	414	28.8
Size cat. unknown	54	3.8
Nodes		
0	1052	73.1
1–3	312	21.7
4+	75	5.2
Outcomes		
Death all cause	124	8.6
Death breast cancer	67	4.7
Ipsilateral event	434	30.2
Contralateral event	234	16.3

Note that all of the women in the Edinburgh breast cancer cohort were treated surgically with BCS.
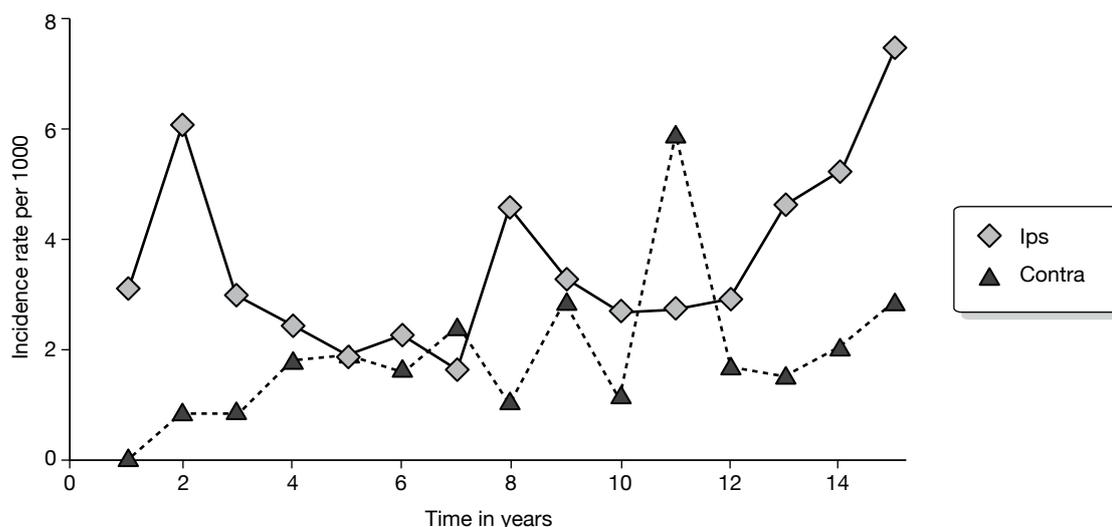
FIGURE 34 Incidence per 1000 per year of ipsilateral recurrence and contralateral occurrence for Edinburgh breast cancer cohort.

TABLE 73 Multiple Cox regression models for IBTR in Edinburgh breast cancer cohort

	n	*N*	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤ 34	15	40	37.5	6.60	3.75 to 11.62	< 0.001	4.65	2.58 to 8.37	< 0.001
35–49	35	308	11.4	1.55	1.02 to 2.35	0.039	1.18	0.77 to 1.80	0.452
50–64	61	826	7.4	(1.00)			(1.00)		
65–74	11	201	5.5	0.81	0.43 to 1.54	0.516	0.77	0.41 to 1.48	0.439
75+	2	64	3.1	0.60	0.15 to 2.47	0.482	0.51	0.12 to 2.09	0.349
Grade									
1	16	363	4.4	(1.00)			(1.00)		
2	55	642	8.6	2.19	1.25 to 3.82	0.006	1.86	1.06 to 3.27	0.030
3	50	402	12.4	3.56	2.03 to 6.26	< 0.001	2.36	1.31 to 4.27	0.004
Unknown	3	32	9.4	2.09	0.61 to 7.16	0.243	1.72	0.49 to 6.07	0.402
Size (mm)									
≤ 10	20	339	5.9	(1.00)			(1.00)		
> 10 to < 20	24	632	3.8	1.23	0.72 to 2.09	0.450	0.90	0.52 to 1.57	0.720
≥ 20	56	414	13.5	2.80	1.68 to 4.67	< 0.001	1.55	0.89 to 2.73	0.124
Size cat. unknown	6	54	11.1	2.14	0.86 to 5.32	0.103	1.53	0.61 to 3.89	0.367
Nodes									
0	69	1052	6.6	(1.00)			(1.00)		
1–3	36	312	11.5	2.02	1.35 to 3.02	0.001	1.75	1.15 to 2.67	0.009
4+	19	75	25.3	5.68	3.41 to 9.45	< 0.001	4.18	2.45 to 7.12	< 0.001

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

**TABLE 74** Multiple Cox regression models for MCBC occurrence in Edinburgh breast cancer cohort

	n	*N*	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤ 34	6	40	6	4.79	2.01 to 11.43	< 0.001	3.94	1.60 to 9.74	0.003
35–49	19	308	19	1.55	0.88 to 2.73	0.128	1.51	0.84 to 2.71	0.165
50–64	33	826	33	(1.00)					
65–74	7	201	7	0.99	0.44 to 2.25	0.990	1.03	0.45 to 2.36	0.936
75–79	2	64	2	1.28	0.30 to 5.34	0.738	1.29	0.31 to 5.49	0.726
Grade									
1	14	363	3.9	(1.00)			(1.00)		
2	25	642	3.9	0.38	0.59 to 2.19	0.695	1.10	0.57 to 2.14	0.769
3	24	402	6.0	0.67	1.03 to 3.86	0.041	1.81	0.90 to 3.64	0.098
Unknown	4	32	12.5	1.95	1.13 to 10.47	0.030	2.61	0.82 to 8.30	0.104
Size (mm)									
≤ 10	17	339	5.0	(1.00)			(1.00)		
> 10 to < 20	27	632	4.3	0.93	0.51 to 1.71	0.817	0.81	0.43 to 1.52	0.508
≥ 20	19	414	4.6	1.13	0.59 to 2.17	0.720	0.83	0.40 to 1.69	0.601
Size cat. unknown	4	54	7.4	1.73	0.58 to 5.15	0.323	1.37	0.45 to 4.16	0.580
Nodes									
0	55	1052	5.2	(1.00)			(1.00)		
1–3	15	312	4.8	1.16	0.65 to 2.06	0.617	1.18	0.65 to 2.15	0.580
4+	1	75	1.3	0.40	0.05 to 2.88	0.362	0.39	0.05 to 2.88	0.357

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 75 Multiple Cox regression models for all-cause death in Edinburgh breast cancer cohort

	n	N	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤ 34	14	40	35.0	1.58	0.92 to 2.71	0.099	0.97	0.55 to 1.70	0.917
35–49	78	308	25.3	0.98	0.76 to 1.27	0.871	0.77	0.59 to 1.00	0.050
50–64	215	826	26.0	(1.00)			(1.00)		
65–74	87	201	43.3	1.90	1.48 to 2.44	< 0.001	1.89	1.47 to 2.44	< 0.001
75–79	40	64	62.5	3.78	2.69 to 5.32	< 0.001	3.33	2.35 to 4.72	< 0.001
Grade									
1	80	363	22.0	(1.00)			(1.00)		
2	193	642	30.1	1.53	1.18 to 1.99	0.001	1.25	0.96 to 1.62	0.105
3	150	402	37.3	2.11	1.61 to 2.77	< 0.001	1.72	1.29 to 2.28	< 0.001
Unknown	11	32	34.4	1.50	0.80 to 2.81	0.210	1.86	0.97 to 3.56	0.061
Size (mm)									
≤ 10	60	339	17.7	(1.00)			(1.00)		
> 10 to < 20	184	632	29.1	1.80	1.35 to 2.41	< 0.001	1.44	1.06 to 1.94	0.018
≥ 20	168	414	40.6	2.76	2.06 to 3.71	< 0.001	1.79	1.30 to 2.47	< 0.001
Size cat. unknown	22	54	40.7	2.58	1.58 to 4.21	< 0.001	1.93	1.16 to 3.20	0.011
Nodes									
0	266	1052	25.3	(1.00)			(1.00)		
1–3	124	312	39.7	1.79	1.44 to 2.21	< 0.001	1.59	1.28 to 1.98	< 0.001
4+	44	75	58.7	3.22	2.33 to 4.45	< 0.001	2.72	1.94 to 3.81	< 0.001
Ipsilateral recurrence									
No	372	1315	28.3	(1.00)					
Yes	62	124	50.0	1.94	1.48 to 2.54	< 0.001	1.87	1.41 to 2.49	< 0.001
Contralateral occurrence									
No	416	1372	30.3	(1.00)			(1.00)		
Yes	18	67	26.9	0.77	0.48 to 1.23	0.277	0.70	0.43 to 1.13	0.140

HR, hazard ratio.

N is the size of the subgroup, *n* is the number of events in that subgroup.

TABLE 76 Multiple Cox regression models for death from breast cancer in Edinburgh breast cancer cohort

	n	*N*	%	Univariate Cox regression			Multiple Cox regression		
				HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)									
≤34	14	40	35.0	2.70	1.55 to 4.69	<0.001	1.17	0.65 to 2.10	0.599
35–49	57	308	18.5	1.25	0.91 to 1.71	0.163	0.89	0.65 to 1.23	0.487
50–64	123	826	14.9	(1.00)			(1.00)		
65–74	27	201	13.4	0.98	0.65 to 1.49	0.935	1.00	0.65 to 1.52	0.987
75–79	13	64	20.3	1.84	1.04 to 3.27	0.037	1.52	0.85 to 2.72	0.160
Grade									
1	26	363	7.2	(1.00)			(1.00)		
2	101	642	15.7	2.38	1.55 to 3.67	<0.001	1.79	1.16 to 2.77	0.009
3	101	402	25.1	4.18	2.71 to 6.43	<0.001	2.86	1.83 to 4.47	<0.001
Unknown	6	32	18.8	2.64	1.08 to 6.41	0.032	3.30	1.32 to 8.21	0.010
Size (mm)									
≤10	21	339	6.2	(1.00)			(1.00)		
>10 to <20	91	632	14.4	2.48	1.55 to 3.99	<0.001	1.86	1.14 to 3.02	0.013
≥20	111	414	26.8	5.07	3.18 to 8.09	<0.001	2.61	1.58 to 4.29	<0.001
Size cat. unknown	11	54	20.4	3.70	1.78 to 7.68	<0.001	2.08	0.96 to 4.48	0.062
Nodes									
0	120	1052	11.4	(1.00)			(1.00)		
1–3	78	312	25.0	2.45	1.84 to 3.26	<0.001	2.05	1.53 to 2.76	<0.001
4+	36	75	48.0	5.50	3.77 to 8.02	<0.001	3.42	2.29 to 5.11	<0.001
Ipsilateral recurrence									
No	179	1315	13.6						
Yes	55	124	44.4	3.59	2.65 to 4.86	<0.001	2.69	1.94 to 3.72	<0.001
Contralateral occurrence									
No	223	1372	16.3	(1.00)					
Yes	11	67	16.4	0.91	0.49 to 1.66	0.747	0.66	0.35 to 1.24	0.199

HR, hazard ratio.
N is the size of the subgroup, *n* is the number of events in that subgroup.

Appendix 27

Example of detailed outline of economic model structure
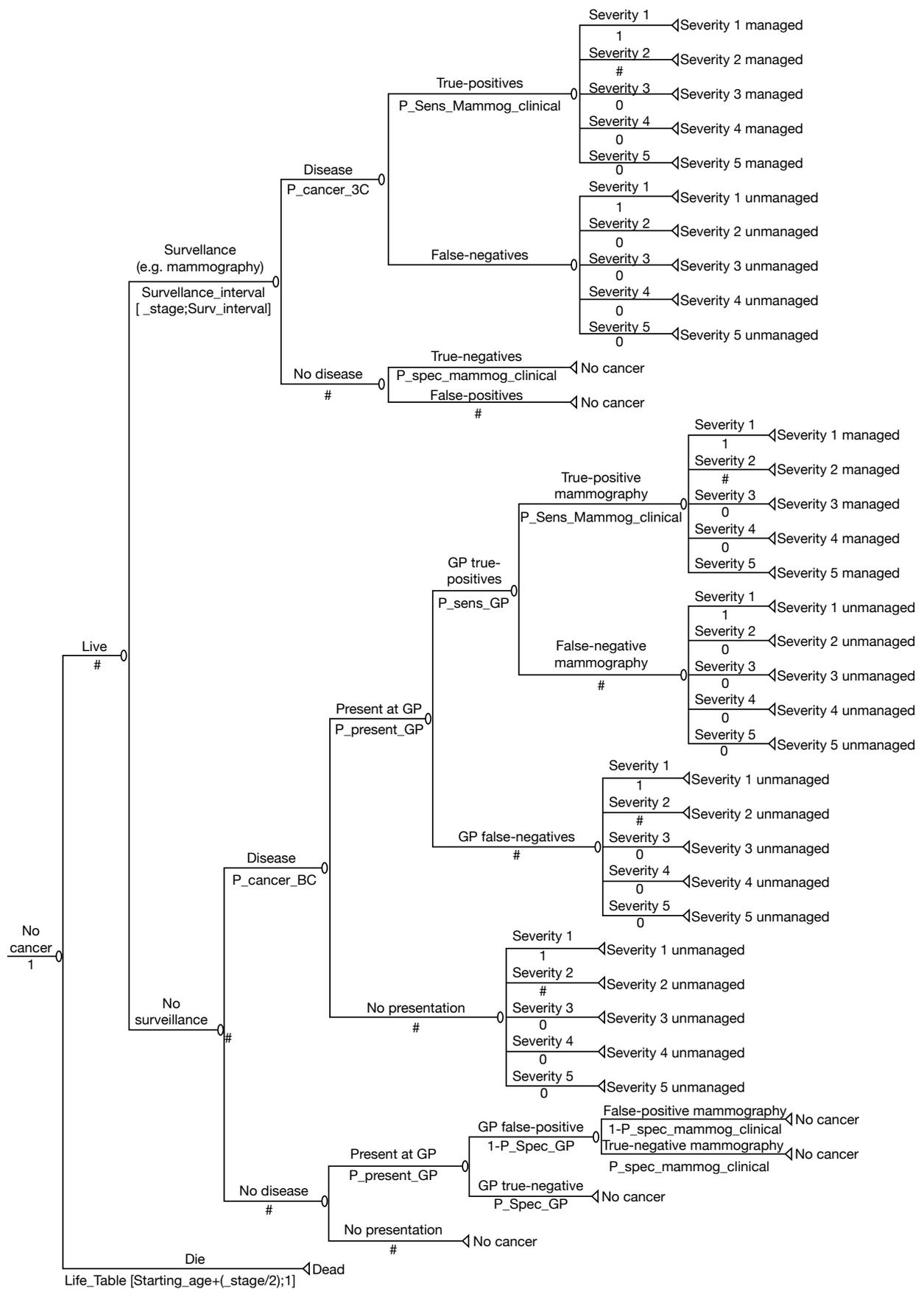
Appendix 28

Review of management guidelines for breast cancer

Overview

In order to assess the cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer, the clinical effectiveness of standard treatment options of any subsequent cancers were required for the economic model.

The objective of this review is to determine the effect of treatment options on survival in patients who are identified as having breast cancer during surveillance. After searching relevant guidelines, the recent updated NICE guideline *Early and Locally Advanced Breast Cancer*, published in February 2009, was identified as providing the best available evidence of treatments for early breast cancer relevant to the UK.[24] This review, therefore, is mainly based on this guideline and the source data used to inform the guideline: the EBCTCG[83] and Adjuvant! Online computer program.[84] Using these sources, estimates of survival following various treatment options were prepared using the Adjuvant! Online computer program due to its flexibility.

Methods

At the beginning of this review, initial scoping searches were carried out into identify relevant local, national or international guidelines. Eleven guidelines were identified describing various treatments or managements of primary breast cancer.[21–25,28,111–115] The most recent of these, and most applicable to the UK, were the NICE guidelines published in February 2009.[24] Few data were available on the effectiveness of treatments for cancers identified following treatment for a primary cancer. As a consequence, it was judged that, in the absence of data in the literature directly relevant to our study question, the best source of information would relate to treatment of primary cancer. It was judged that, of the guidelines available, the best available summary of existing evidence on the clinical effectiveness of treatments of breast cancer, including early, locally advanced and advanced disease, was provided by the NICE guidelines. The literature searches used to inform these guidelines considered papers published up to July 2008.

NICE guideline: Early and Locally Advanced Breast Cancer

The NICE guideline *Early and Locally Advanced Breast Cancer*,[24] published in February 2009, updated and developed guidance from three NICE technology appraisals: 109 (docetaxel), 108 (paclitaxel) and 107 (trastuzumab).[99,116,117] The evidence on clinical effectiveness of diagnoses and treatments for early and locally advanced breast cancer is based on the systematic review of relevant clinical literatures and critical appraisal.

Search strategy

Papers that were published or accepted for publication in peer-reviewed journals were considered as relevant. Search filters, such as those to identify systematic reviews and RCTs, were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed

(unless of particular importance to the question). Any evidence published before July 2008 was included. The following databases were included in the literature search:

- The Cochrane Library
- MEDLINE and PREMEDLINE 1950 onwards
- Excerpta Medica (EMBASE) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1994 onwards
- PsycINFO 1806 onwards
- Web of Science 1970 onwards [specifically SCI Expanded and Social Sciences Citation Index (SSCI)]
- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- BioMed Central 1997 onwards
- NRR
- CCT.

Types of studies included in the guideline

Relevant guidelines, systematic reviews and RCTs of different treatments for early or locally advanced breast cancer. In the absence of RCT evidence, the observational studies were considered in the review such as cohort, case–controls, etc.

Types of interventions considered in the guideline

Table 77 summarises the treatment interventions included in the NICE guideline. Surgery is considered as the first line of treatment in primary breast cancer, such as mastectomy, BCT and surgery to the axilla. Adjuvant therapies were used in management of breast cancer after the surgery, including hormonal therapy, chemotherapy, biological therapy and radiotherapy.

Critical appraisal of studies included in the NICE guideline

One researcher independently scanned the titles and abstracts of every article. Full texts were obtained for any papers that were considered potentially relevant or where there was insufficient information. The researcher then applied the inclusion/exclusion criteria to determine which studies were relevant. Included papers were critically appraised and data extracted. Quality assessment was based on the SIGN criteria.

Summary

The NICE guideline overviewed the best clinical evidence of treatment options derived from the studies that it reviewed and appraised.[24] In addition to BCS or mastectomy, adjuvant treatments are used and the selection of adjuvant therapies depends on tumour factors (ER and HER2 status) and patient characteristics (age and menopausal status). However, the NICE guideline did not report the detailed data but rather made a recommendation on the use of adjuvant treatments. The guideline suggested that two sources were more likely to provide reliable data on the effectiveness of adjuvant treatments: (1) a series of overviews and meta-analyses of different treatments in the EBCTCG that provides the effectiveness of adjuvant treatment after surgical therapy for early breast cancer, and (2) Adjuvant! Online, based on a US population, to estimate the efficacy of adjuvant therapies (hormonal or chemotherapy) after initial surgical treatment.

Effect of adjuvant treatments on survival based on overview in EBCTCG

The NICE guideline suggested that overviews of meta-analyses in EBCTCG appear to provide the best evidence for estimating risk for treating breast cancer in the UK. The EBCTCG was established in 1984. The most recent publications from the EBCTCG relate to:

TABLE 77 Treatments considered in the NICE guideline

Interventions	Population setting: early and locally advanced breast cancer	Studies
Surgery to breast	DCIS	33 observation studies
Mastectomy		
Breast-conserving therapy		
Surgery to the axilla		Invasive breast cancer SLNB vs clearance or axillary sampling: 33 RCTs and case series, a systematic review (69 studies)
Sentinel lymph node biopsy (SNLB)		
		Axillary sampling as staging surgery: 15 studies (two RCTs, 13 case series)
Adjuvant endocrine therapy (hormonal)	Invasive disease with hormone receptor positive	
Tamoxifen	ER alpha positive	
Aromatase inhibitors:		
Anastrozole	ER or PR positive	Nine RCTs
Letrozole	ER or PR positive	Five RCTs
Exemestane	ER or PR positive	Four RCTs
Adjuvant chemotherapy		A meta-analysis from EBCTCG
Docetaxel	Early lymph node positive	Four RCTs, one Cochrane, a HTA report, a meta-analysis, a pooled analysis
Paclitaxel	Early lymph node positive	Four RCTs, one Cochrane, a HTA report, a meta-analysis, a pooled analysis
Taxanes		Two RCTs, a meta-analysis and a pooled analysis, a TACT study
Adjuvant biological therapy	HER2 receptor positive	
Humanised monoclonal antibody (trastuzumab)		Four RCTs (HERA, NSABP B-31, NCCTG N9831 and E2198)
Adjuvant radiotherapy	Invasive breast, DCIS	
BCS and radiotherapy	Invasive breast, DCIS	One RCT, two non-RCTs, three reviews and four guidelines for invasive, three studies (two RCTs, one retrospective) for DCIS
Postmastectomy radiotherapy		EBCTCG and five additional RCTs
Primary systematic therapy		Three systematic reviews of RCTs and a published review
Neoadjuvant endocrine therapy		One systematic review of RCTs
Neoadjuvant chemotherapy		One systematic review of RCTs and a published review
Neoadjuvant radiotherapy		

PR, progesterone receptor; SNLB, sentinel lymph node biopsy.

- adjuvant polychemotherapy in ER-poor breast cancer: meta-analysis of individual patient data from the randomised trials[118]
- chemotherapy and hormonal therapy for early breast cancer: effects on recurrence and 15-year survival in an overview of the randomised trials[3]
- effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.[2]

Some adjuvant treatments tested in the 1980s have clear evidence that they substantially reduce 5-year recurrence rates and also substantially reduce 15-year overall mortality rates (e.g. tamoxifen, polychemotherapy regimens and radiotherapy). Further improvements in long-term

survival could be available from newer drugs, or better use of older drugs. The reviews, however, although excellent, do not provide data readily useable in an economic model, as it is not possible to estimate survivals for specific types of cancer. However, for completeness a summary of key findings is presented below.

Adjuvant chemotherapy

The number of randomised trials of chemotherapy increased substantially over the first two decades of the EBCTCG overview, with a shift from trials comparing chemotherapy with no chemotherapy, to trials of different types of chemotherapy. In the first cycle of the overview, 31 randomised trials of no chemotherapy versus chemotherapy using one or more drugs were included. This involved a total of 9000 women, of whom 2900 had died. Subsequent cycles refined this to focus on trials of prolonged multiagent chemotherapy. By the third cycle of the EBCTCG overview, this analysis was based on 18,000 women from 47 trials, and it had risen further to 60 trials (29,000 women and 10,000 deaths) by the fourth cycle. The recent meta-analysis from randomised trials is to assess the long-term effects of adjuvant polychemotherapy regimens in ER-poor breast cancer, and the extent to which these effects are modified by age or tamoxifen use.[118] This study analysed 6000 patients with ER-poor breast cancer in 46 trials of polychemotherapy against not, and about 14,000 women with ER-poor breast cancer in 50 trials of tamoxifen versus not.

Adjuvant hormonal therapy

The first EBCTCG review of tamoxifen, in the mid-1980s, included data from a total of 16,500 women in 28 randomised trials, of whom nearly 3800 were known to have died. This grew to 40 trials (30,000 women and 8200 deaths) in the second cycle; and then to 55 trials, involving > 12,000 deaths among 37,000 women. By the 2000–5 cycle of the EBCTCG overview, the growth in the number of trials included had levelled off at 56, but further accrual to some of these trials and five more years of follow-up for many of them meant that the number of women in the analysis had increased to 48,000, with a total of 18,000 deaths.[3] This represented 88% of the total number of women randomised into eligible trials of adjuvant tamoxifen versus no immediate tamoxifen worldwide.

Adjuvant radiotherapy

The most recent overview of radiotherapy and differences of surgery published in 2005[2] was based on the analysis of 42,000 women in 78 randomised treatment comparisons (radiotherapy vs no radiotherapy, 23,500; more surgery vs less surgery, 9300; more surgery vs radiotherapy, 9300). A total of 24 types of local treatment comparison were identified to help relate the effect on local (i.e. locoregional) recurrence to that on breast cancer mortality.

Effect of treatments on survival for breast cancer using the Adjuvant! Online computer program

Adjuvant! Online is a tool of assessment of risk of an individual patient developing recurrent disease and/or dying within 10 years. Adjuvant! Online draws information from mortality statistics in the USA, the SEER database, and meta-analyses and individual clinical trials. Based on well-validated factors, such as age, menopausal status, ER status, tumour size and grade, nodes status, etc., predictions can be made about survival for alternative adjuvant treatment regimens, such as chemotherapy, endocrine, etc. However, survival estimates are derived from the US population. Version 8 of this tool may underestimate the risk of mortality and the benefit of trastuzumab in HER-2-positive patients. *Table 78* describes the information used to predict recurrence and mortality.

TABLE 78 Prognostic factors in Adjuvant! Online

Comorbidity	Perfect	Minor problems	Average for age	Major 10	Major 20	Major 30
ER status	Undefined	Positive	Negative			
Tumour size (cm)	0.1–1	1.1–2	2.1–3	3.1–5	>5	
Positive nodes	0	1–3	4–9	>9		
Tumour grade	Undefined	1	2	3		
Age (years)	1–99					

The NICE guideline summarised the following issues in its critical appraisal of this tool:

■ The predictions made by Adjuvant! Online are based on the published methodology, which has been updated periodically as evidence of treatment effectiveness and data on risk factors become available.

■ Help files and published descriptions of the tool make clear some of the assumptions and limitations that underpin the methodology. The impact of these individual assumptions is difficult to assess. Adjuvant! Online deals with key uncertainties by alerting the user to them at relevant points.

■ Survival estimates are derived from the US population. Quantifying the impact on survival of socioeconomic background and of ethnic differences between US and UK populations is difficult.

■ Adjuvant! Online is already used in the UK and is designed to incorporate the Oxford overview meta-analyses.

■ The strongest evidence of Adjuvant! Online validity for the UK is derived from comparisons between predictions and observed outcomes using a Canadian population. This study found its predications to be reliable for most groups. Further validation is under way using a European population.

Survival estimates for treatment options using the Adjuvant! Online computer program

Adjuvant! Online integrates patient-related information (age and comorbidity) and tumour-related information (nodal status, tumour size, histological grade, ER status and histological subtype) to make estimates of mortality caused by cancer or from other causes. *Table 79* reports an example of mortality estimates for a woman with breast cancer depending upon her characteristics and tumour factors when the woman is 40 years old, has perfect health, tumour grade is undefined and oestrogen status is positive.

Summary

Decisions on the treatment for every woman with breast cancer should be based on the best evidence. This requires a combination of information about the patient and tumour along with evidence on the effectiveness of the treatments being considered. This evidence needs to be as reliable as possible. It was judged by the research team that the NICE guideline *Early and Locally Advanced Breast Cancer* provided the best available summary of evidence of breast cancer treatments. However, the NICE guideline did not report estimates of clinical effectiveness of treatment options. Based on the NICE guideline, there are two reliable sources that produce the

TABLE 79 Mortality rate when age=40 years

Patient and tumour characteristics				Mortality at 10 years								
				No adjunctive therapy (%)			Hormonal (%)		Chemotherapy (%)		Combined (%)	
Comorbidity	ER status	Tumour size (cm)	Positive nodes	Total	Cancer	Other	Total	Cancer	Total	Cancer	Total	Cancer
None	Positive	0.1–1.0	0	4.3	3.0	1.3	3.4	2.1	3.5	2.2	2.8	1.5
			1–3	22.1	20.9	1.2	16.0	14.8	16.4	15.2	11.9	10.7
			4–9	41.9	40.8	1.1	31.0	29.9	31.8	30.7	23.3	22.2
			>9	65.6	64.7	0.9	51.4	50.5	53.4	52.5	39.9	39.0
		1.1–2.0	0	9.3	8.0	1.3	6.8	5.5	6.9	5.6	5.2	3.9
			1–3	22.1	20.9	1.2	16.0	14.8	16.4	15.2	11.9	10.7
			4–9	41.9	40.8	1.1	31.0	29.9	31.8	30.7	23.3	22.2
			>9	65.6	64.7	0.9	51.4	50.5	52.4	51.5	39.9	39.0
		2.1–3.0	0	21.1	19.9	1.2	15.7	14.5	15.3	14.1	11.4	10.2
			1–3	40.9	39.8	1.1	30.3	29.2	31.0	29.9	22.7	21.6
			4–9	56.7	55.7	1.0	43.7	42.7	44.3	43.3	33.2	32.2
			>9	75.4	74.6	0.8	61.1	60.3	62.2	61.4	48.5	47.7
		3.1–5.0	0	28.1	26.9	1.2	20.3	19.1	20.8	19.6	15.2	14.0
			1–3	40.9	39.8	1.1	30.3	29.2	31.0	29.9	22.7	21.6
			4–9	56.7	55.7	1.0	43.4	42.4	44.3	43.3	33.2	32.2
			>9	76.4	75.6	0.8	62.1	61.3	63.2	62.4	49.5	48.7
		>5.0	0	32.0	30.8	1.2	23.3	22.1	23.9	22.7	17.4	16.2
			1–3	53.7	52.7	1.0	40.8	39.8	41.7	40.7	31.1	30.1
			4–9	70.5	69.7	0.8	56.1	55.3	57.2	56.4	44.1	43.3
			>9	87.2	86.6	0.6	74.7	74.1	75.7	75.1	61.7	61.1

estimates of effectiveness of adjuvant treatments: EBCTCG overviews and Adjuvant! Online. Of these Adjuvant! Online was sufficiently flexible to allow relevant data to be estimated for the economic model. Estimates from Adjuvant! Online provide similar/dissimilar estimates to the EBCTCG overviews, which, arguably, are more applicable to a UK population. However, as EBCTCG overview subset analyses are carried out largely as a set of univariate subset analyses it is impossible to tell if two univariate effects are independent.

Adjuvant! Online integrates patient-related information (age and comorbidity) and tumour-related information (nodal status, tumour size, histological grade, ER status and histological subtype) to make estimates of mortality and recurrence. However, survival estimates are derived from the US population.

Appendix 29

Estimates of the different types of cancer that exist

Categories

Size (mm)	Grade	Nodes	Vascular invasion	Count	Total	Percentage
0–20	1	0	No	3207	3326	12.28
			Yes	119		
		1–3	No	503	589	2.18
			Yes	86		
		4+	No	54	88	0.32
			Yes	34		
	2	0	No	4522	5178	19.12
			Yes	656		
		1–3	No	1031	1471	5.43
			Yes	440		
		4+	No	253	450	1.66
			Yes	197		
	3	0	No	2105	2695	9.95
			Yes	590		
		1–3	No	491	916	3.38
			Yes	425		
		4+	No	161	462	1.71
			Yes	301		
20.001–49.999	1	0	No	477	528	1.95
			Yes	51		
		1–3	No	209	283	1.05
			Yes	74		
		4+	No	59	109	0.40
			Yes	50		
	2	0	No	1781	2233	8.25
			Yes	452		
		1–3	No	912	1541	5.69
			Yes	629		
		4+	No	392	1018	3.76
			Yes	626		
	3	0	No	1526	2209	8.16
			Yes	683		
		1–3	No	628	1467	5.42
			Yes	839		
		4+	No	292	1256	4.64
			Yes	964		

Categories

Size (mm)	Grade	Nodes	Vascular invasion	Count	Total	Percentage
50+	1	0	No	22	24	0.09
			Yes	2		
		1–3	No	11	15	0.06
			Yes	4		
		4+	No	9	26	0.10
			Yes	17		
	2	0	No	92	110	0.41
			Yes	18		
		1–3	No	105	172	0.64
			Yes	67		
		4+	No	95	280	1.03
			Yes	185		
	3	0	No	76	118	0.44
			Yes	42		
		1 –3	No	44	161	0.59
			Yes	117		
		4+	No	45	355	1.31
			Yes	310		
			Total	**27,080**		**100**

Appendix 30

Summary of data from Adjuvant! Online used – estimated 10-year survival

Risk profile level	Definition	Mortality % (range)	10-year mortality (adjuvant actual)	Total % in each category (ER+ and ER−)	Total in category adjusting for ER status-	Treatment	Notes
1	ER+, G1, TS 0.1–2.0, 0 node	1–3	2	12.3	8.61	Hormone	
	ER+, G2, TS 0.1–2.0, 0 nodes	4–6	5.5	19.1	13.37	Hormone	
	ER+, G1, TS 2.1–5.0, 0 nodes	4–6	6.1	1.9	1.33	Hormone	
	ER+, G1, TS 0.1–2.0, 1–3 nodes	4–6	4.4	2.20	1.54	Hormone+chemo	
	ER−, G1, TS 0.1–2.0, 0 nodes	4–6	6	12.3	3.69	Nothing	
	ER+, G3, TS 0.1–2.0, 0 nodes	4–6	6.4	10	7	Hormone+chemo	
					35.54	*4.86 = average for risk profile 1*	
2	ER+, G2, TS2.1–5.0, 1–3 nodes	16–18	18.5	5.7	3.99	Hormone+chemo	
	ER−, G1,TS 0.1–2.0, 1–3 nodes	7–9	9.3	2.2	0.66	Chemo	
	ER+, G2, TS 0.1–2.0, 1–3 nodes	7–9	8.6	5.4	3.78	Hormone+chemo	
	ER−, G3, TS 0.1–2.0, 0 nodes	10–12	12.1	10	3	Chemo	
	ER+, G2, TS 2.1–5, 0 nodes	10–12	11.9	8.2	5.74	Hormone	
	ER+, G1, TS 2.1–5.0, 1–3 nodes	10–12	10.1	1	0.7	Hormone+chemo	
	ER+, G1, TS 0.1–2.0, 4–9 nodes	10–12	11.2	0.3	0.21	Hormone+chemo	
	ER+, G3, TS 2.1–5.0, 0 nodes	10–12	12.3	8.2	5.74	Hormone+chemo	
					23.82	*12.47 = average for risk profile 2*	

Risk profile level	Definition	Mortality % (range)	10-year mortality (adjuvant actual)	Total % in each category (ER+ and ER−)	Total in category adjusting for ER status-	Treatment	Notes
3	ER+, G2, TS >5.0, 0 nodes	13–15	14.6	0.4	0.28	Hormone+chemo	
	ER+, G3, TS 0.1–2.0, 1–3 nodes	13–15	15.7	3.4	2.38	Hormone+chemo	
	ER+, G1, TS 2.1–5.0, 4–9 nodes	16–19	16.2	0.4	0.28	Hormone+chemo	
	ER−, G1, TS 2.1–5.0, 0 nodes	13–15	15.9	1.9	0.57	Nothing	15% harm?
	ER−, G2, TS 0.1–2.0, 0 nodes	13–15	13.9	19.1	5.73	Nothing	15% harm?
	ER+, G2, TS 0.1–2.0, 4–9 nodes	16–19	17.3	1.7	1.19	Hormone+chemo	
	ER−, G1,TS 0.1–2.0, 4–9 nodes	22–24	22.8	0.3	0.09	Chemo	15% harm?
	ER−, G1, TS 2.1–5.0, 1–3 nodes	22–24	22	1	0.3	Chemo	15% harm?
	ER−, G2, TS 0.1–2.0,1–3 nodes	22–24	22	5.4	1.62	Chemo	15% harm?
	ER−, G3, TS 0.1–2.0, 1–3 nodes	22–24	24.3	3.4	1.02	Chemo	15% harm?
	ER−, G3, TS 2.1–5.0, 0 nodes	22–24	22.8	8.2	2.46	Chemo	15% harm?
	ER+, G3, TS >5.0, 0 nodes	16–19	19.1	0.4	0.28	Hormone+chemo	
	ER− G1, TS >5.0, 0 nodes	22–24	22.9	0.09	0.027	Hormone	15% harm?
	ER+, G3, TS 2.1–5.0, 1–3 nodes	22–24	24.7	5.4	3.78	Hormone+chemo	
	ER+, G2, TS 2.1–5.0, 4–9 nodes	22–24	24.7	3.8	2.66	Hormone+chemo	
					22.67	*19.65 = average for risk profile 3*	

Risk profile level	Definition	Mortality % (range)	10-year mortality (adjuvant actual)	Total % in each category (ER+ and ER−)	Total in category adjusting for ER status-	Treatment	Notes
4	ER−, G1, TS 2.1–5.0, 4–9 nodes	28–30	28.2	0.4	3.384	0.12	Chemo	15% chemo?
	ER−, G2, TS 2.1–5.0, 0 nodes	28–30	28.8	8.2	70.848	2.46	Hormone	If large ,chemo?
	ER+, G1, TS >5.0, 0 nodes	28–30	28.2	0.09	1.7766	0.063	Hormone	Chemo?
	ER−, G1, TS >5.0,1–3 nodes	28–30	29.8	0.06	0.5364	0.018	Chemo	15% horm?
	ER−, G3, TS >5.0, 0 nodes	28–30	29.8	0.4	3.576	0.12	Chemo	15% horm?
	ER+, G2, TS >5.0,1–3 nodes	25–27	25.3	0.6	10.626	0.42	Hormone+chemo	
	ER+, G1, TS 2.1–5.0, 9+ nodes	28–30	28	0.4	7.84	0.28	Hormone+chemo	
	ER+, G3, TS 0.1–2.0, 4–9 nodes	28–30	29.3	1.7	34.867	1.19	Hormone+chemo	
	ER+, G1, TS >5.0,1–3 nodes	28–30	29.8	0.06	1.2516	0.042	Hormone+chemo	
				4.713	*28.58 = average for risk profile 4*		
5	ER+, G1, TS 0.1–2.0, 9+ nodes	31–33	32.2	0.32	7.2128	0.224	Chemo	
	ER+, G2, TS 0.1–2.0, 9+ nodes	31–33	31.4	1.7	37.366	1.19	Hormone+chemo	
	ER+, G3, TS >5.0,1–3 nodes	31–33	33.6	0.6	14.112	0.42	Hormone+chemo	
	ER+, G2, TS >5.0,4–9 nodes	31–33	33.6	1	23.52	0.7	Hormone+chemo	
				2.534	*32.44 = average for risk profile 5*		
6	ER−, G2, TS 0.1–2.0, 4–9 nodes	34–36	34	1.7	17.34	0.51	Chemo	15% horm?
	ER+, G2, TS 2.1–5.0, 9+ nodes	37–39	38.2	3.8	101.612	2.66	Hormone+chemo	
	ER+, G3, TS 0.1–2.0, 9+ nodes	37–39	38.6	1.7	45.934	1.19	Hormone+chemo	
	ER+, G3, TS 2.1–5.0, 4–9 nodes	37–39	37.4	4.6	120.428	3.22	Hormone+chemo	
	ER−, G1, TS 0.1–2.0, 9+ nodes	37–39	39.9	0.3	3.591	0.09	Chemo	15% horm?
	ER−, G3, TS 2.1–5.0, 1–3 nodes	37–39	39.9	5.4	64.638	1.62	Chemo	15% horm?
	ER−, G2, TS 2.1–5.0, 1–3 nodes	34–36	36.4	5.7	62.244	1.71	Chemo	15% horm?
	ER−, G1, TS >5.0, 4–9 nodes	37–39	38.1	0.1	1.143	0.03	Chemo	15% horm?
	ER−, G2, TS >5.0, 0 nodes	37–39	37.8	0.4	4.536	0.12	Nothing	15% horm?
				11.15	*37.80 = average for risk profile 6*		

Risk profile level	Definition	Mortality % (range)	10-year mortality (adjuvant actual)	Total % in each category (ER+ and ER−)	Total in category adjusting for ER status-	Treatment	Notes
7	ER−, G1,TS 2.1–5.0, 9+ nodes	46–48	46	0.4	0.12	5.52	Chemo	15% horm?
	ER−, G3, TS 0.1–2.0, 4–9 nodes	46–48	46.9	1.7	0.51	23.919	Chemo	15% horm?
	ER−, G2, TS 0.1–2.0, 9+ nodes	49–51	51.5	1.7	0.51	26.265	Chemo	15% horm?
	ER−, G2, TS 2.1–5.0, 4–9 nodes	46–48	46.9	3.8	1.14	53.466	Chemo	15% horm?
	ER−, G2, TS >5.0, 1–3 nodes	46–48	47.9	0.6	0.18	8.622	Chemo	15% horm?
	ER−, G3, TS >5.0, 1–3 nodes	49–51	51.5	0.6	0.18	9.27	Chemo	15% horm?
	ER+, G1, TS >5.0, 4–9 nodes	49–51	51.2	0.1	0.07	3.584	hormone+chemo	
	ER+, G2, TS >5.0, >9 nodes	49–51	49.6	1	0.7	34.72	Hormone+chemo	
	ER+, G3, TS >5.0, 4–9 nodes	46–48	48.6	1.3	0.91	44.226	Hormone+chemo	
	ER+, G3, TS 2.1–5.0, 9+ nodes	49–51	51.6	4.6	3.22	166.152	Hormone+chemo	
					7.54	49.83 = average for risk profile 7		
8	ER−, G3, TS 2.1–5.0, 4–9 nodes	52–54	52.5	4.6	1.38	72.45	Chemo	15% horm?
	ER−, G2, TS 2.1–5.0, 9+ nodes	58–60	60.4	3.8	1.14	68.856	Chemo	15% horm?
	ER−, G3, TS 0.1–2.0, 9+ nodes	64–66	66.8	1.7	0.51	34.068	Chemo	15% horm?
	ER−, G3, TS 2.1–5, 9+ nodes	73–75	75.1	4.6	1.38	103.638	Chemo	15% horm?
	ER+, G1, TS >5.0, >9 nodes	67–69	68.3	0.1	0.07	4.781	Hormone+chemo	
	ER+, G3, TS >5.0, >9 nodes	64–66	65.2	1.3	0.91	59.332	Hormone+chemo	
	ER−, G1, TS >5.0, >9 nodes	58–60	59.4	0.1	0.03	1.782	Chemo	15% horm?
	ER−, G2, TS >5.0, 4–9 nodes	58–60	60.4	1	0.3	18.12	Chemo	15% horm?
	ER−, G2, TS >5.0, >9 nodes	73–75	73.8	1	0.3	22.14	Chemo	15% horm?
	ER−, G3, TS >5.0, 4–9 nodes	64–66	65.7	1.3	0.39	25.623	Chemo	15% horm?
	ER−, G3, TS >5.0, >9 nodes	86 +	86.6	1.3	0.39	33.774	Chemo	15% horm?
					6.8	65.38 = average for risk profile 8		

TS, tumour size.

Assumptions

Decision rules for treatment

1. ER+ = hormone therapy
2. Grade 3 = chemotherapy
3. ER+ and positive nodes = hormone + chemotherapy
4. ER−, 0 nodes = nothing
5. ER− = chemotherapy (15% might get hormone therapy in addition)

Appendix 31

All-cause mortality rates

Index (cycle)	Value	Index (cycle)	Value
0	0.002185889	43	0.000633701
1	0.000176516	44	0.000670725
2	9.65047E-05	45	0.000765293
3	8.05032E-05	46	0.00082434
4	5.85017E-05	47	0.000914418
5	4.80012E-05	48	0.001034035
6	4.90012E-05	49	0.001076079
7	4.10008E-05	50	0.00128032
8	4.5001E-05	51	0.001346907
9	3.90008E-05	52	0.001431525
10	4.65011E-05	53	0.001580249
11	4.85012E-05	54	0.001770067
12	5.00013E-05	55	0.001879266
13	5.90017E-05	56	0.002072648
14	5.95018E-05	57	0.002197414
15	7.90031E-05	58	0.002361288
16	8.65037E-05	59	0.002655025
17	0.000122508	60	0.002852067
18	0.000135509	61	0.00323122
19	0.000128508	62	0.003459484
20	0.000120507	63	0.003906631
21	0.000132009	64	0.004267104
22	0.000131509	65	0.004599578
23	0.000123508	66	0.005054775
24	0.000147011	67	0.005641413
25	0.00014351	68	0.006184122
26	0.000168514	69	0.006790556
27	0.000155512	70	0.007564612
28	0.000179016	71	0.00831507
29	0.000190518	72	0.009229593
30	0.000208022	73	0.010470819
31	0.000203021	74	0.011811253
32	0.00024353	75	0.013020264
33	0.000269536	76	0.01471527
34	0.000287541	77	0.016491993
35	0.000299045	78	0.018562279
36	0.000322052	79	0.021135862
37	0.000363566	80	0.023809957
38	0.000397579	81	0.026686587
39	0.000448601	82	0.029678404
40	0.00049012	83	0.033678625
41	0.000528139	84	0.037974533
42	0.000575666	85	0.04250483

Index (cycle)	Value
86	0.047340565
87	0.05188872
88	0.058742862
89	0.06434889
90	0.072877031
91	0.083887561
92	0.093932122
93	0.104376753
94	0.114247213
95	0.125022286
96	0.13718484
97	0.146604429
98	0.163656171
99	0.172317694
100	0.188410202

Appendix 32

Summary of findings of the structured review of doubling times

The identified papers are summarised in *Table 80* and described below. Peer and colleagues[89] conducted a study in the Netherlands using data from the Breast Screening Programme from the period 1980–91 to determine the growth rate of primary breast cancer stratified by age. The authors report the mean breast cancer doubling times by age, based on information from 236 cancers with a measurable tumour nucleus (*Table 81*). The authors reported that tumour doubling time was age dependent, with those of a younger age having a shorter tumour doubling time. In addition to the data reported in *Table 81* the authors also present doubling times for other studies. Doubling times from these studies range from a low of 60 days[119] to 268 days.[120]

Spratt[121] undertook a study to determine the association of doubling times of primary breast cancer and other histopathological and mammography characteristics. The study was undertaken at the University of Louisville Breast Cancer Detection and Demonstration Project (BCDDP). The data used consisted of 23 tumours with doubling times ranging from 109 days to 944 days (median 324 days). The authors found an association between faster growth rate and three factors, one of which was the nuclear grade of tumour; however, no information was presented on the actual increased doubling time by grade. A further study[88] used data from both the University of Louisville and University of Heidelberg of women who had undergone routine mammography as part of a breast-screening programme. In total, 448 observations were obtained and used to measure the growth rate of tumours. The authors found that the median doubling time was 260 days (mean age 53 years). A large variation in doubling time was observed, however, ranging from 10 days to 7051 days.

Arnerlöv and colleagues[122] analysed the doubling time of tumours based on information from 158 patients with breast cancer who were diagnosed between 1974 and 1987 in Sweden. The authors found large variations in tumour doubling rates. The median doubling time was 11 months. In contrast with Spratt's study, the authors found no association between doubling time and grade, although they did find that short doubling times were significantly correlated with tumour size.

In a recent study, Weedon-Fekjaer and colleagues[123] used a likelihood-based estimating procedure to estimate tumour growth, using data from the Norwegian Breast Cancer Screening Programme. The data relate to 503 women aged between 50 and 69 years, over the period 1985–94. The authors found a large variation in tumour growth rates, with 5% of tumours taking < 1.2 months to double in size from 10 to 20 mm. At the other extreme, the authors found that 5% of tumours had a doubling time of 6.3 years. Mean tumour doubling time was found to be 1.7 years, with doubling time increasing with age. Overall, evidence from these studies shows a large variation in doubling times.

Brekelmans and colleagues[124] conducted a study based on data from a breast-screening programme in the Netherlands. The results were based on 104 invasive tumours detected between 1975 and 1986. The mean doubling time was reported to be 99 days (range 6–309 days).

TABLE 80 Summary of studies reporting data on doubling times of breast cancer

Author (date) Location	Methods	Results
Peer *et al.* (1993)[89] Nijmegen, Netherlands	Study based on data from the Breast Cancer Screening Programme conducted in the Netherlands since 1975. The study data are from the period 1980–91 and are based on 236 cancers with measurable tumour nucleus	The tumour doubling time was found to be age dependent: < 50 years' doubling time was 80 days (95% CI 44 to 147 days)
	The authors calculated the doubling time of tumours by age group: < 50 years (*n* = 32 cancers); 50–70 years (*n* = 154 cancers); > 70 years (*n* = 50 cancers)	50–70 years' doubling time was 157 days (95% CI 121 to 204 days)
		> 70 years' doubling time 188 days (95% CI 120 to 295)
Brekelmans *et al.* (1996)[124] Netherlands	Study based on data from a breast-screening programme (DOM project) in the Netherlands	The mean doubling time of the whole group was 99 days (range 6–309 days)
	Based on 139 cancers detected between 1975 and 1986. After exclusions the analysis was based on 104 invasive tumours	By subgroup analysis this was: 51 days in the masked group
	The analysis was subdivided into four groups: missed cancers; masked cancers; intermediate growth rate; and fast growth rate	128 days in the intermediate group 79 days in the fast-growing group
Arnerlöv *et al.* (1992)[122] Sweden	Study analyses the doubling time of tumours based on information form 158 patients with breast cancer who were diagnosed between 1974 and 1987	The mean age of patients was 65 years. The authors found variations in the tumour doubling rate (0.6 months to indefinite time). Median doubling time was 11 months (approximately 330 days) and mean doubling time was 10.9 months
Spratt *et al.* (1993)[88] Heidelberg and Louisville	Used data (from both Heidelberg and Louisville) of women who had undergone routine mammography as part of a breast-screening programme. In total, 448 observations were obtained and used to measure the growth rate of breast cancers	The mean age of patients was 53 years. The authors found the median doubling time to be 260 days, ranging from the shortest doubling time of 10 days to 7051 days
Spratt (1981)[121] University of Louisville	Spratt undertook a study to determine the association of doubling times of primary breast cancer and other histopathologic and mammography characteristics. The study was undertaken at the University of Louisville Breast Cancer Detection and Demonstration Project (BCDDP)	The data used consisted of 23 tumours with doubling times ranging from 109 to 944 days (median 324 days). The authors found an association between faster growth rate and three factors, one of which was the nuclear grade of tumour; however, no information was presented on the actual increased doubling time by grade
Tilanus-Linthorst *et al.* (2007)[125] UK, the Netherlands and Canada	Analysed breast cancer growth rates found during screening for patients in the UK, Holland and Canada. The authors were able to assess doubling time of tumours in 100 cases. These cases were subdivided into *BRCA1* mutation (43 women); *BRCA2* mutation (16 women) and high risk (41 women)	The authors found an inverse relationship between growth rate and age. The authors grouped their analysis into three age groups: ≤ 40, 41–50 and > 50 years There were differences in doubling times between the subgroups by severity and age: doubling time in *BRCA1/2* mutations in the three age categories was 28, 68 and 81 days, respectively
		In the high-risk group, without mutations, the doubling time in the three age groups was 83, 121 and 173 days, respectively
Weedon-Fekjaer *et al.* (2008)[123] Norway	The authors used a likelihood-based modelling method to estimate the growth rate of cancers using mammography screening data. The data pertains to 503 women aged between 50 and 69 years over the period 1985–94	The authors found large variation in the growth rates of tumours
		In women aged 50–59 years the mean doubling time (from 10 to 20 mm) was 1.4 years. This increased to 2.1 years in women aged 60–69 years
		Over both age groups this was estimated to be 1.7 years (SD 2.2 years)

TABLE 81 Mean breast cancer doubling times by age

Age at diagnosis (years)	Mean (95% CI)
< 50	80 (44 to 147) days
50–70	157 (121 to 204) days
> 70	188 (120 to 295) days

Source: Peer and colleagues.[89]

Tilanus-Linthorst and colleagues[125] analysed breast cancer growth rates found during screening patients in the UK, Holland and Canada. The authors assessed doubling time of tumours in 100 cases. These cases were subdivided into *BRCA1* mutation (43 women), *BRCA2* mutation (16 women) and high risk (41 women). The mean age of patients was 65 years. The authors found variations in the tumour doubling rate (0.6 months to indefinite time). Median doubling time was 11 months (approximately 330 days) and mean doubling time was 10.9 months.

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