Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment (HTA) of surveillance of women aged less than 50 years at elevated risk of breast cancer

Technical Report

19 March 2013

Safer Better Care

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is the independent Authority established to drive continuous improvement in Ireland's health and personal social care services, monitor the safety and quality of these services and promote person-centred care for the benefit of the public.

The Authority's mandate to date extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting to the Minister for Health and the Minister for Children and Youth Affairs, the Health Information and Quality Authority has statutory responsibility for:

- **Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for those health and social care services in Ireland that by law are required to be regulated by the Authority.

- **Social Services Inspectorate** – Registering and inspecting residential centres for dependent people and inspecting children detention schools, foster care services and child protection services.

- **Monitoring Healthcare Quality and Safety** – Monitoring the quality and safety of health and personal social care services and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health Technology Assessment** – Ensuring the best outcome for people who use our health services and best use of resources by evaluating the clinical and cost effectiveness of drugs, equipment, diagnostic techniques and health promotion activities.

- **Health Information** – Advising on the efficient and secure collection and sharing of health information, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care services.

Foreword

Breast cancer is the most common invasive cancer diagnosed in women in Ireland and the second most common cause of cancer death in women. Although the majority of breast cancers are sporadic, it is estimated that 25% of cases relate to a familial risk with 5% to 10% of all cases specifically relating to a genetic predisposition. Cancers relating to genetic predisposition have a median age of onset more than 20 years earlier than the general population. The lifetime risk of developing breast cancer is 10% to 11% for the general population; for female carriers of mutations of the *BRCA1* and *BRCA2* genes, average lifetime rates of up to 60% to 80% are reported.

Screening and surveillance are secondary preventive measures that aim to detect breast cancer at the earliest possible stage in order to reduce the rate of breast cancer death. Screening refers to monitoring those at average risk of a disease; surveillance refers to the monitoring of those known to be an increased risk of the disease. Internationally recommended surveillance imaging options include digital mammography, magnetic resonance imaging (MRI) or a combination of the two. However, there is currently no consensus as to the optimal design of a surveillance programme.

The Director of the National Cancer Control Programme (NCCP) in the Health Service Executive (HSE) requested that the Health Information and Quality Authority (the Authority or HIQA) undertake a health technology assessment (HTA) in relation to a potential national surveillance programme for women aged less than 50 years at elevated risk of breast cancer due to a familial or genetic predisposition. The purpose of this HTA is to examine the safety, effectiveness, cost-effectiveness, budget impact, and resource implications of a surveillance programme based on digital mammography, magnetic resonance imaging (MRI) or a combination thereof.

Work on the assessment was undertaken by an Evaluation Team from the HTA Directorate of the Authority. A multidisciplinary Expert Advisory Group (EAG) was convened to advise the Authority during the conduct of this assessment.

The Authority would like to thank its Evaluation Team, the members of the EAG and all who contributed to the preparation of this report.

Dr Máirín Ryan,
Director of Health Technology Assessment,
Health Information and Quality Authority

Table of Contents

Acknowledgements

The Authority would like to thank all of the individuals and organisations who provided their time, advice and information in support of this health technology assessment (HTA).

Particular thanks are due to the Expert Advisory Group (EAG), Dr David Gallagher (Mater Misericordiae University Hospital, Dublin), Dr Andrew Green (National Centre for Medical Genetics in Our Lady's Children's Hospital, Crumlin, Dublin), James O'Mahony (PhD fellow, Trinity College, Dublin), Dr Niall Sheehy (St James's Hospital, Dublin) and the individuals within the organisations listed below who provided advice.

The membership of the EAG was as follows:

Professor Peter Daly, Consultant Medical Oncologist, nominated by the Royal College of Physicians of Ireland

Dr Barbara Dunne, Consultant Pathologist, St James's Hospital, Dublin, nominated by the Faculty of Pathology, Royal College of Physicians of Ireland

Ms Naomi Fitzgibbon, Public representative, nominated by the Irish Cancer Society*

Mr Martin Flattery, Head of HTA Research and Planning, Health Information and Quality Authority*

Dr Patricia Harrington, Head of Assessment, Health Information and Quality Authority

Dr Niamh Hambly, Consultant Radiologist, Beaumont Hospital, Dublin, nominated by the Faculty of Radiologists, Royal College of Surgeons in Ireland

Dr Deirdre Madden, Faculty of Law, University College Cork

Professor Andrea Manca, Professor of Health Economics, University of York, UK

Ms Mairead Lyons, Public representative, nominated by the Irish Cancer Society*

Mr Ray McLaughlin, Consultant Surgeon, University College Hospital, Galway, nominated by the Royal College of Surgeons in Ireland

Dr Sorcha McNally, Consultant Radiologist, BreastCheck Merrion Unit, nominated by the Faculty of Radiologists, Royal College of Surgeons in Ireland

Dr Deirdre Mulholland (Chair), Head of Standards and Methodology, Health Information and Quality Authority*

Dr Deirdre Murray, Specialist in Public Health Medicine, National Cancer Control Programme

Ms Laura O'Donoghue, Clinical Nurse Specialist, Mid-Western Regional Hospital Limerick, nominated by the Irish Association of Nurses in Oncology

Mr Colm Power, Consultant Surgeon, Beaumont Hospital, Dublin, nominated by the Royal College of Surgeons in Ireland

Dr Máirín Ryan (Chair), Director of Health Technology Assessment, Health Information and Quality Authority*

Dr Conor Teljeur, Senior Mathematician/Statistician, Health Information and Quality Authority

Dr Clare Smith, Consultant Radiologist, Mater Misericordiae University Hospital, Dublin, nominated by the National Cancer Screening Service

Dr Linda Sharp, Epidemiologist, National Cancer Registry Ireland

Dr Valerie Walshe, Senior Health Economist, Health Service Executive

Ms Dympna Watson, Patient representative, nominated by Europa Donna

* Martin Flattery left the Authority in February 2012; Ms Mairead Lyons was replaced by Ms Naomi Fitzgibbon in September 2012; Dr Deirdre Mulholland was replaced by Dr Máirín Ryan in September 2012

Organisations that assisted the Authority in providing information, in writing or through meetings, included:

Beaumont Hospital

Cork University Hospital

Health Service Executive (HSE)

Mayo General Hospital

National Cancer Registry Ireland

National Cancer Screening Service

National Centre for Medical Genetics

Mater Misericordiae University Hospital

Mid-Western Regional Hospital Limerick

St James's Hospital

University Hospital Galway

Waterford Regional Hospital

Members of the Evaluation Team:

Members of the Authority's Evaluation Team included: Martin Flattery,^ Dr Patricia Harrington, Patrick Moran, Dr Linda Murphy, Michelle O'Neill, Dr Conor Teljeur and Dr Máirín Ryan.

^ Martin Flattery left the Authority in February 2012

Conflicts of Interest

None reported.

List of abbreviations that appear in this report

ACER	Average cost-effectiveness ratio
AR-DRG	Australian refined diagnosis related groups
BIA	Budget impact analysis
***BRCA1* gene**	Breast cancer 1, early onset gene[(1)]
***BRCA2* gene**	Breast cancer 2, early onset gene[(2)]
CBE	Clinical breast examination
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness analysis curve
CI	Confidence interval
CUA	Cost-utility analysis
DMX	Digital mammography
EAG	Expert Advisory Group
ER	(O)estrogen receptor
ESRI	Economic and Social Research Institute
FMX	Film mammography
HER2	Human epidermal growth factor receptor 2
HIPE	Hospital In-Patient Enquiry Scheme
HSE	Health Service Executive
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
MRI	Magnetic resonance imaging
NCCP	National Cancer Control Programme
NCRI	National Cancer Registry Ireland
NCSS	National Cancer Screening Service, Ireland
NICE	National Institute for Health and Care Excellence, UK
PACS	Picture archiving and communication system
PR	Progesterone receptor
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SD	Standard deviation
TP53	Tumour protein 53 gene

1. Introduction to the Technical Report

1.1 Background to request

On 28 July 2011, the Director of the National Cancer Control Programme (NCCP) in the Health Service Executive (HSE), Dr Susan O'Reilly, requested that the Health Information and Quality Authority (the Authority or HIQA) undertake a health technology assessment (HTA) in relation to surveillance mammography and magnetic resonance imaging (MRI) in women less than 50 years of age known to be at elevated risk of breast cancer because of either a genetic predisposition or a strong family history.

The request for a formal HTA was on foot of a recommendation from an Expert Advisory Group on Hereditary Cancer convened by the National Cancer Screening Service Board.[3] The primary task of this group was to review and evaluate international evidence regarding best practice in the assessment and management of hereditary cancer risk, specifically in relation to breast and colorectal cancer. It identified the considerable debate nationally and internationally concerning the age at which surveillance should commence, the most appropriate imaging methodology, the frequency of surveillance, and the cost-effectiveness of such surveillance.

In Ireland, breast cancer is the most common invasive cancer diagnosed in women. It accounted for 32.3% of all invasive cancers in the period 2007-09 with an average of 2,673 new cases diagnosed each year. The median age at diagnosis is 59 years. After lung cancer, breast cancer is the second most common cause of cancer death in women (611 deaths, 15.8% of the total in 2007); the median age at death is 72 years.[4] One quarter of cases are diagnosed in women aged less than 50 years of age, with 15% of deaths occurring in this age group.

The majority of cases of breast cancers are sporadic occurring in women with no apparent family history. International data suggest that approximately 25% of breast cancer incidence is due to familial risk.[5] Genetic predisposition is an important risk factor accounting for 5% to 10% of all breast cancers. Of these, 50% are attributable to two main high penetrance breast cancer genes, *BRCA1* and *BRCA2*.[5] The lifetime risk of developing breast cancer by the age of 80 years is up to 87% in female carriers of a *BRCA1* or *BRCA2* mutation, compared to 10% to 11% in the general population.[6;7] Cancers due to genetic predisposition are associated with an early age of onset, having a median age of diagnosis more than 20 years earlier than for the general population.[8] Approximately 45% of cases of early-onset breast cancer (age at diagnosis ≤ 40 years) may be linked to *BRCA1*.[6]

Screening and surveillance are secondary preventive measures that aim to detect breast cancer at the earliest possible stage. Screening refers to monitoring individuals at an average risk of disease; surveillance refers to monitoring those known to be at an increased risk. When followed by appropriate diagnosis and treatment, randomised controlled trials of population screening programmes using mammography in women at average risk of breast cancer have shown a reduction in mortality from breast cancer.[9-11] It is assumed that surveillance will confer a similar reduction in mortality in women at elevated risk of breast cancer.[12] Screening is not recommended for women under the age of 50 years that have an average risk of breast cancer. However, surveillance is considered appropriate in women who have an elevated risk of breast cancer given their high lifetime risk and that many of these cancers develop between 35 and 50 years of age.

Several recommendations have been published regarding breast cancer surveillance in women at elevated risk of breast cancer, with the guidelines being based on expert opinion. Recommended imaging surveillance typically includes mammography, or MRI or a combination of the two. However, there is no current consensus regarding the optimal age at which surveillance should begin, the frequency of this surveillance or the choice of imaging technique(s).

1.2 Terms of Reference

Based on the available evidence, the NCCP will consider if there should be a national surveillance programme for women aged less than 50 years at elevated risk of breast cancer. In consultation with the NCCP, key questions in relation to the age at which surveillance should commence, the frequency of surveillance, and the most appropriate imaging methodology were developed. Answers to these questions, which underpinned the Terms of Reference of this HTA, will inform the decision of the NCCP.

The Terms of Reference were:

- Describe the epidemiology of breast cancer for those under the age of 50 at high and moderate risk of hereditary breast cancer (due to genetic predisposition or strong family history).
- Review the evidence of the effectiveness and safety of mammography, MRI surveillance and a combination of the two in the specified population(s) including both different surveillance frequencies and age groups.
- Examine the cost-effectiveness of these surveillance options compared to the current practice of no organised surveillance programme and relative to each other.
- Estimate the budget impact of the introduction of a surveillance programme for the selected population(s).

- Identify the key additional resources necessary in order to implement a surveillance programme as effectively and efficiently as possible.
- Consider any additional impact that a surveillance programme is likely to have including wider ethical or societal implications for the healthcare system or for affected families.

The specific remit of this HTA was to assess the issue of surveillance using digital mammography, MRI, or a combination thereof in women aged less than 50 years at elevated risk of breast cancer. The HTA used as its basis the framework report developed by the Expert Advisory Group on Hereditary Cancer Risk.[3] This outlined the agreed definitions of 'moderate' and 'high' risk, the standardised risk assessment model to be used across family risk clinics in Ireland, and the referral pathways for women aged less than 50 years identified to be at an average, moderate or high risk of breast cancer. These risk classifications were used in the HTA to identify those at elevated risk of breast cancer.

It was acknowledged that there are others at elevated risk of breast cancer for which surveillance is also indicated. This includes individuals with an iatrogenic risk of breast cancer secondary to moderate to high doses of therapeutic radiation to the whole body, mantle field, mediastinum, lung and thorax for Hodgkin lymphoma and a range of paediatric and young adult cancers.[13] However, these individuals are at risk of other long-term complications including disorders of the thyroid, heart and lung and require more comprehensive long-term surveillance. The management of these individuals was beyond the scope of this HTA as it was considered that their breast cancer surveillance should take place within a dedicated comprehensive programme.

1.3 Overall approach

Following an initial scoping of the technology, the Terms of Reference of this assessment were agreed between the Authority and the National Cancer Control Programme (NCCP) of the Health Service Executive (HSE).

The Authority convened an Expert Advisory Group (EAG) comprising representation from relevant stakeholders including the HSE, the National Cancer Registry Ireland, clinicians with specialist expertise, representatives of patients' organisations, an ethics expert and an international health technology assessment expert. The role of the EAG was to inform and guide the process, provide expert advice and information and to provide access to data where appropriate. A full list of the membership of the EAG is available in the acknowledgements section of this report. The Terms of Reference of the EAG were to:

- Contribute to the provision of high quality and considered advice by the Authority to the Health Service Executive.
- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to the Authority regarding the scope of the analysis.
- Support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

The Authority appointed an Evaluation Team comprised of internal staff from the HTA directorate to carry out the assessment.

The Terms of Reference of the HTA were agreed by the EAG at the initial meeting of the group. Interim findings from the assessment and issues to be addressed, including the parameters for the cost-effectiveness model, were discussed at subsequent meetings. A final draft report was reviewed by the EAG and subsequently approved by the Board of the Authority prior to submission to the National Cancer Control Programme of the HSE and the Minister for Health.

2 Burden of disease

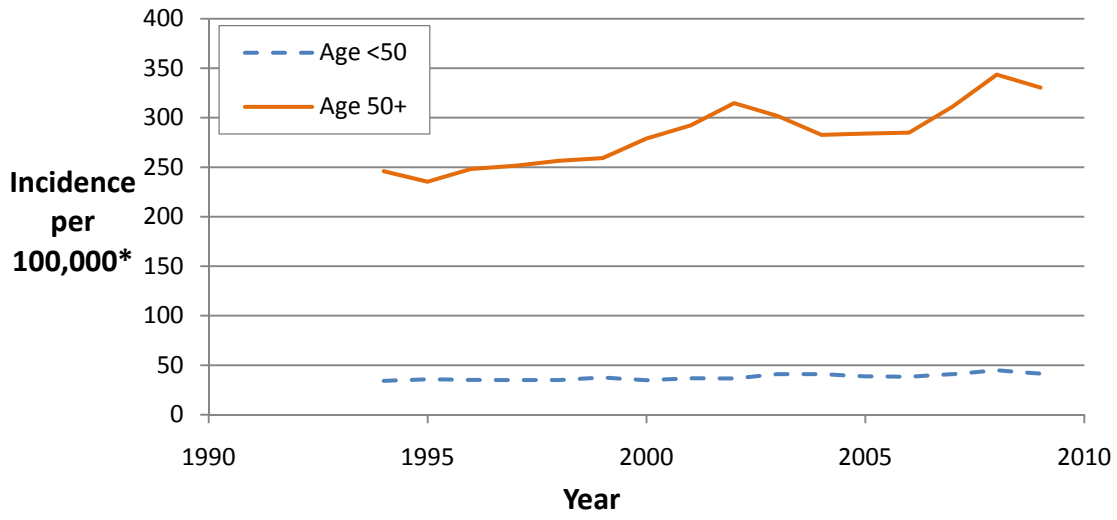
This chapter describes the epidemiology of female breast cancer in Ireland in terms of incidence, mortality and survival. Risk categories are also discussed, and estimates of the numbers of women in different risk categories are presented.

2.1 Incidence

Breast cancer is the most commonly diagnosed invasive cancer in women in Ireland.[4] From 2007 to 2009, on average 2,673 new cases of invasive female breast cancer were diagnosed each year. Over the same period, there was an average of 658 new cases of breast cancer each year in women under the age of 50. Between 2002-2004 and 2007-2009, the number of new cases of female breast cancer across all ages and in women under 50 increased by 22% and 20%, respectively. Ireland ranks fourth highest in Europe in terms of incidence of female breast cancer.

The incidence of breast cancer increased in Ireland from 1994 to 2002. Nationally, breast cancer screening is provided for women aged 50-64 years through BreastCheck, a population-based screening programme. BreastCheck was introduced in the eastern part of the country in 2000, expanded to the south and west in 2007 and became available nationally from late 2009. The first round of screening from 2000 to 2002 resulted in an initial rise in numbers due to the rapid detection of prevalent cancers. From 2002 to 2006 the incidence decreased to reach what would have been the expected level of incidence based on pre-2000 trends (see Figure 2.1).

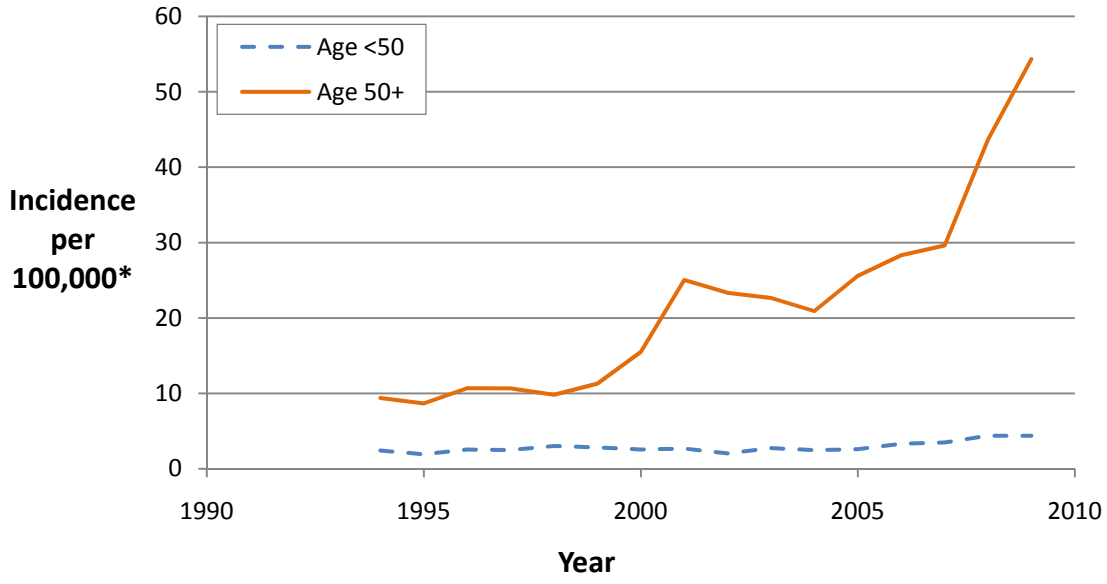
Figure 2.1 Age-standardised incidence rates of female breast cancer per 100,000 population by year of diagnosis, Ireland 1994-2009



** Data: National Cancer Registry Ireland, age-standardised to the European Standard Population.*

Ductal carcinoma in situ (DCIS) is a form of non-invasive breast cancer. It is less commonly diagnosed than invasive breast cancer and is rarely clinically palpable or symptomatic. By definition, DCIS refers to cells that have become cancerous, but still reside in their normal place in the breast ducts. DCIS is a non-lethal form of cancer, but is frequently a precursor to invasive cancer.[14] The adoption of screening programmes has led to increased detection and treatment of DCIS.[15] These in situ cancers accounted for 21% of all cancers detected through the BreastCheck programme in 2009. On average, 260 women were diagnosed with non-invasive breast cancer each year in Ireland between 2005 and 2009. The age standardised incidence rate increased by 8% per annum between 1994 and 2007; and by 30% per annum between 2007 and 2009. In 2009, 178 of the 383 in situ breast cancers reported nationally were diagnosed through the BreastCheck screening programme.[16;17] The impact of the roll-out of the national screening programme can be seen on the changes in DCIS incidence since 2000 in women aged 50 and over (see Figure 2.2).

Figure 2.2 Age-standardised incidence rates of ductal carcinoma in situ of the female breast per 100,000 population by year of diagnosis, Ireland 1994-2009

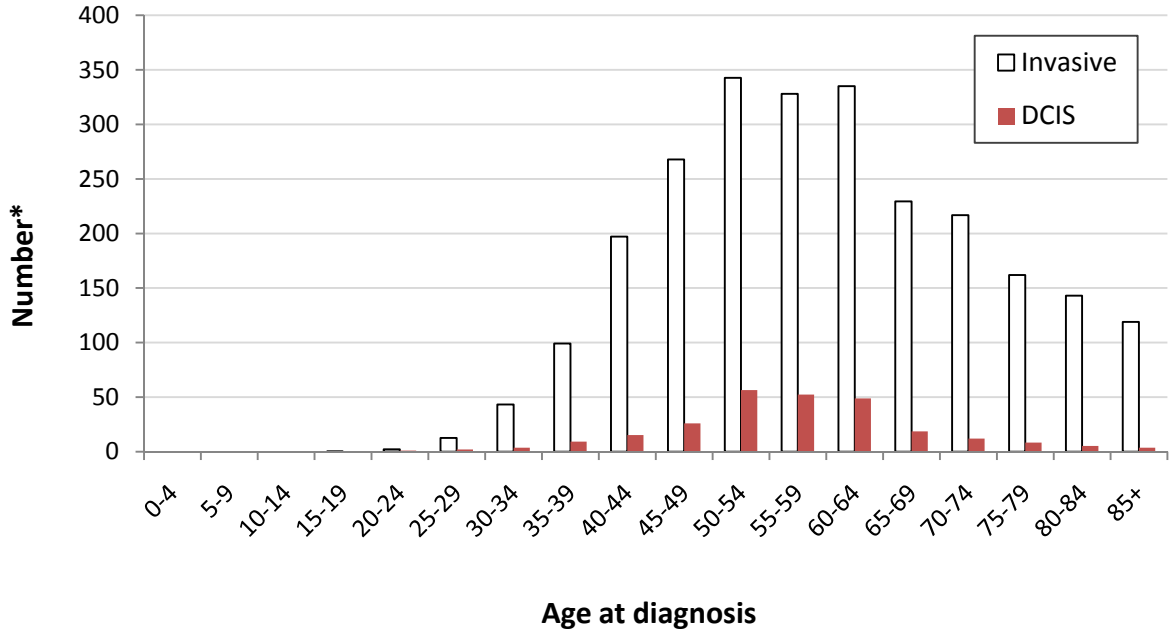


** Data: National Cancer Registry Ireland, age-standardised to the European Standard Population.*

The average annual incidence of female breast cancer by age at diagnosis for the period 2005-2009 is shown in Figure 2.3. Incidence of invasive female breast cancer is projected to increase in the coming decades.[18] However, much of this increase will be attributable to women aged 65 years and older. Incidence in women aged less than 45 years is predicted to double by 2035 while incidence in the 45-54 age band is predicted to increase gradually before declining after 2030 to return to

current levels by 2040. Across all ages, there will be a predicted 3% increase in incidence per annum due to demographic changes alone.

Figure 2.3 Average annual number of cases of female breast cancer by age at diagnosis, 2005-2009



* *Data: National Cancer Registry Ireland.*

The stage of a breast cancer depends on the size of the cancer; whether the cancer is invasive or non-invasive; whether the cancer is in the lymph nodes; and the presence of distant metastasis. Stage at diagnosis is an important predictor of treatment success and survival. In Ireland, during the period 2006-2010, 31% of all female breast cancer cases were stage I, 44% were stage II, 12% were stage III, 7% were stage IV, and 6% were of unknown stage (see Table 2.1). These figures are based on the assumption that missing information on N and M stage is null, thereby reducing the proportion at unknown stage.

Table 2.1 Overall stage distribution of female breast cancer in Ireland (2006-2010) and stratified by age*[19]

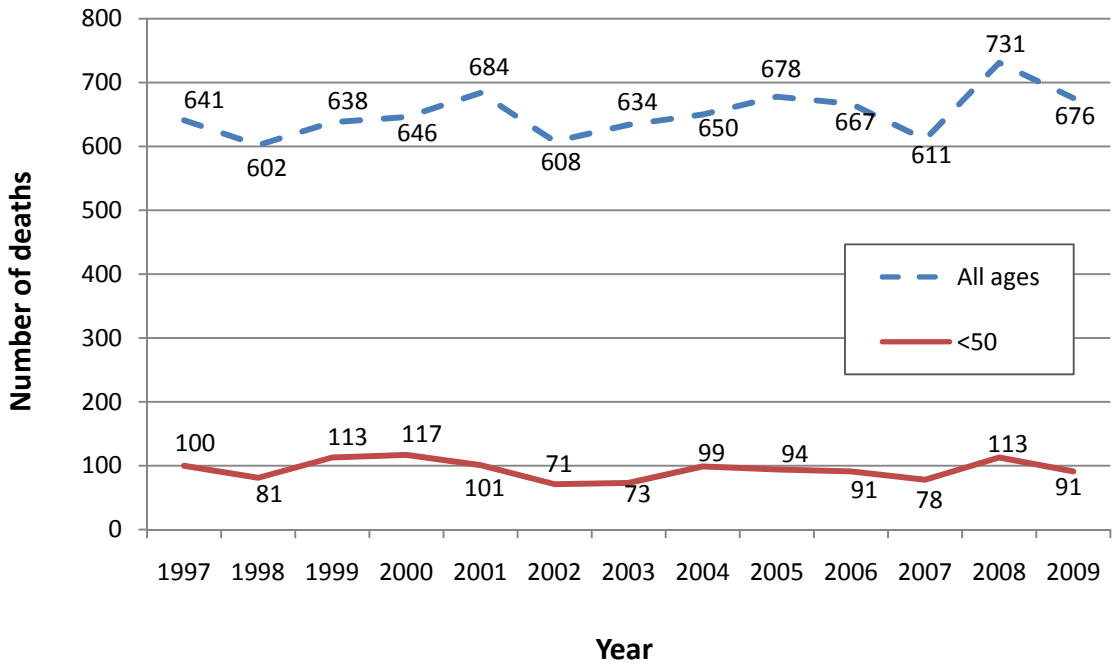
Stage	% cases overall	% cases aged <50 years	% cases aged 50 years +	Primary Tumour Status**	Regional Lymph Node Status**	Distant Metastasis Status**
Stage I	31	26	32	T1	N0	M0
				T0	N1mi	M0
				T1	N1mi	M0
Stage II	44	47	41	T0	N1	M0
				T1	N1	M0
				T2	N0	M0
				T2	N1	M0
				T3	N0	M0
Stage III	12	14	12	T0	N2	M0
				T1	N2	M0
				T2	N2	M0
				T3	N1	M0
				T3	N2	M0
				T4	N0	M0
				T4	N1	M0
				T4	N2	M0
				Any T	N3	M0
Stage IV	7	6	6	Any T	Any N	M1
Unknown	6	7	9	-	-	-

* *Data: National Cancer Registry Ireland.*
** For explanation of T, N and M classification see American Joint Committee on Cancer.[19]

2.2 Mortality

Women aged less than 50 years account for 25% of invasive breast cancer incidence, but less than 10% of deaths. Between 2000 and 2009, an average of 659 women died each year from breast cancer. The median age at death was 72 years.[4] In women aged less than 50 years, there has been an average of 88 deaths per year between 2005 and 2010 (Figure 2.4).

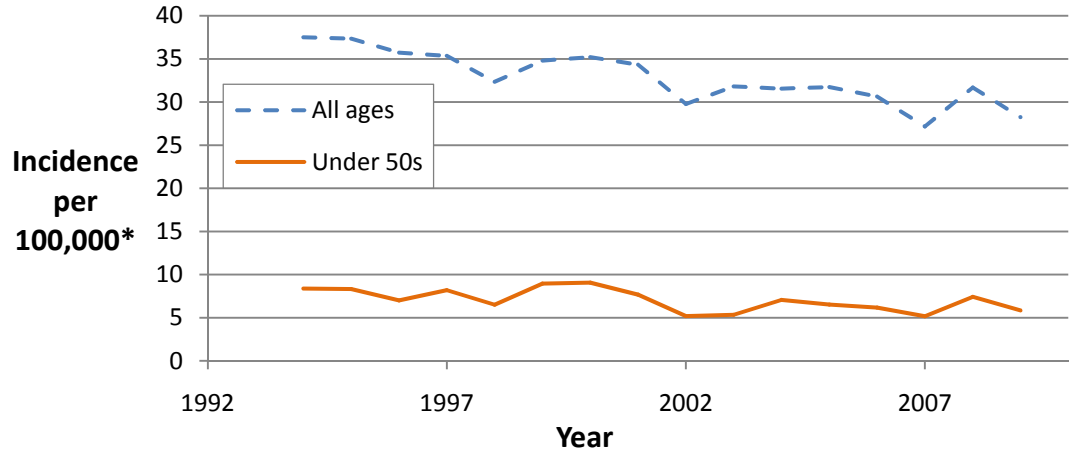
Figure 2.4 Numbers of deaths from invasive female breast cancer by year, Ireland 1997-2009



Data: National Cancer Registry Ireland.

When mortality is age-standardised, rates have been decreasing since the early 1990s, although the reduction has been modest in women aged less than 50 years (Figure 2.5).

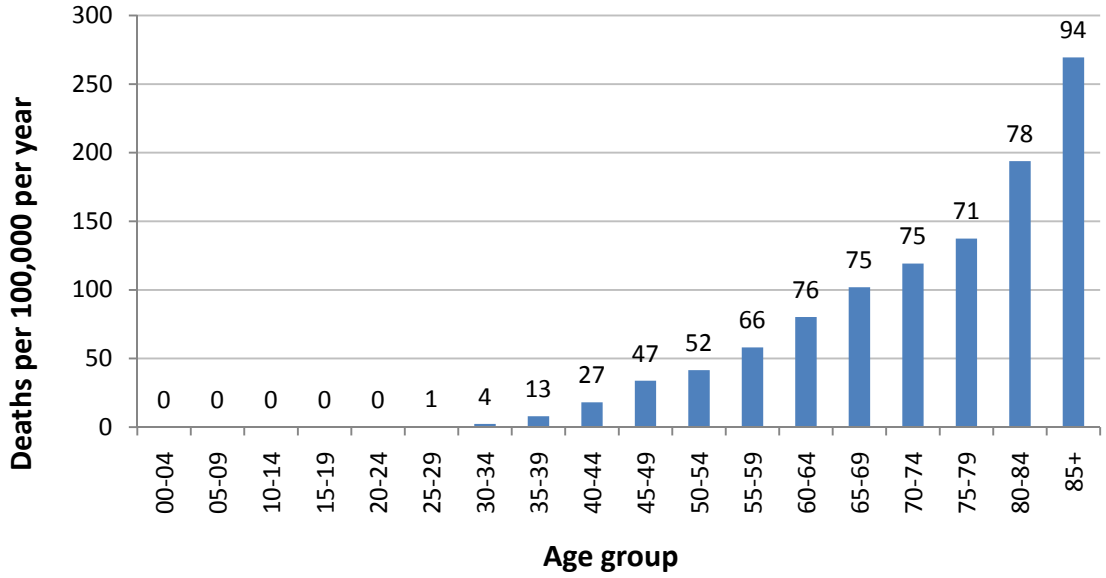
Figure 2.5 Age-standardised mortality rates of invasive female breast cancer per 100,000 population by year of death, Ireland 1994-2009



* Age-standardised to the European Standard Population
Data: *National Cancer Registry Ireland.*

The mortality rate increases rapidly with age, with deaths before the age of 30 being very rare. Almost half of all deaths occur in women aged 70 years and older (see Figure 2.6). According to 2008 data, Ireland has the fourth highest breast cancer mortality rate in Europe, behind Belgium, Denmark and the Netherlands.[4]

Figure 2.6 Invasive female breast cancer deaths per 100,000 per year by age group, Ireland 2005-2009

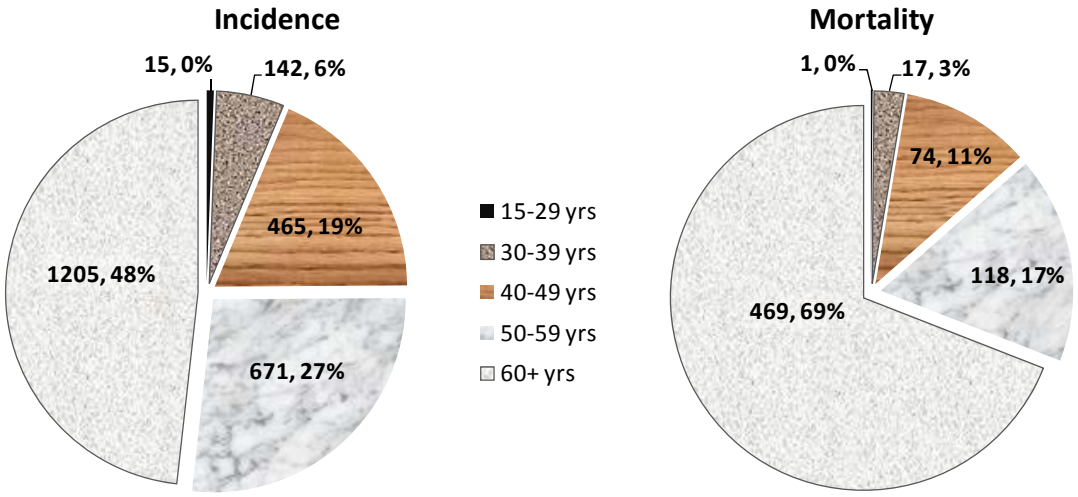


Data labels represent average annual number of deaths 2005-2009

Data: Central Statistics Office.

The relative contribution of each age band to incidence and mortality is shown in Figure 2.7. Although women aged less than 50 years account for 25% of incidence, they account for only 14% of mortality.

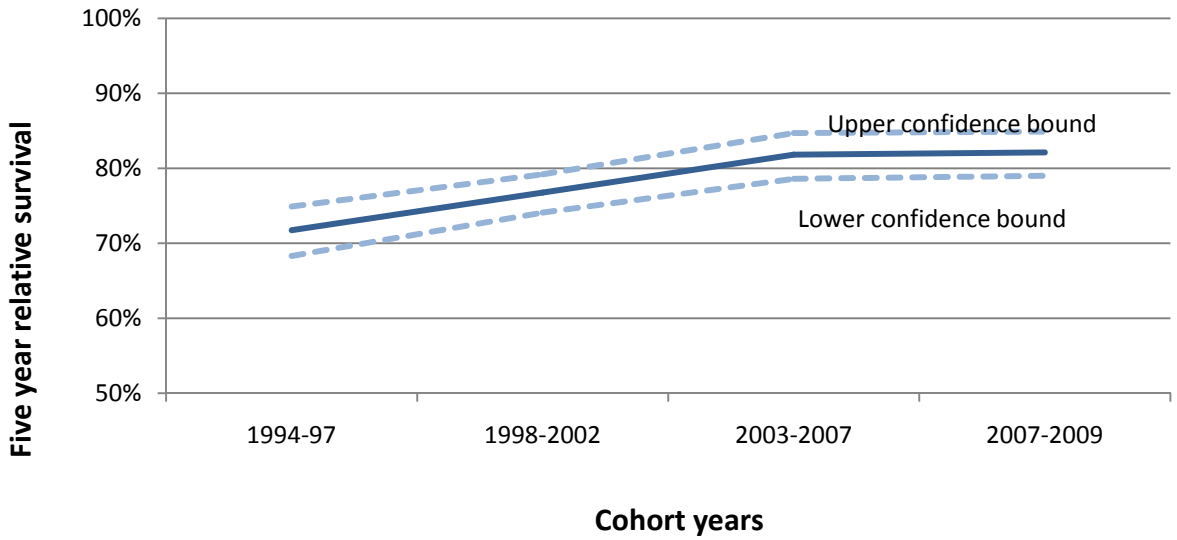
Figure 2.7 Incidence and mortality from invasive female breast cancer by age group, Ireland 2009



2.3 Survival

The percentage of patients alive five years after diagnosis with invasive breast cancer has improved over time (Figure 2.8). In 2007-2009, the average percentage surviving to five years was 85%, compared to 74% in 1994-1997. The highest survival rates are observed in the 45 to 54 year olds, with the lowest survival rates in those aged 75 years and older.

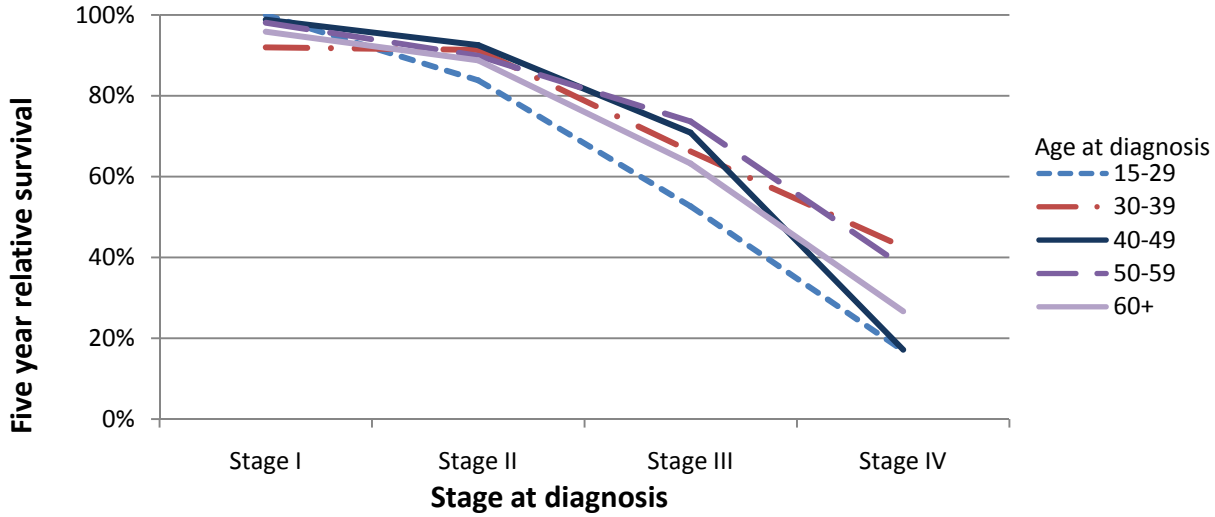
Figure 2.8 Five-year relative survival for invasive female breast cancer by year of diagnosis (1994-2009)



Data: National Cancer Registry Ireland.

The probability of five-year-survival is strongly linked to stage at diagnosis (Figure 2.9). Those diagnosed at stage I have 98.9% survival to five years, compared to 27.7% in those diagnosed at stage IV. The relative drop in five-year-survival by stage at diagnosis is equivalent across age groups.

Figure 2.9 Five-year relative survival for invasive female breast cancer by age and stage at diagnosis (2003-2007)



Data: National Cancer Registry Ireland.

Survival for those with breast cancer in Ireland has historically been low compared to that of our European counterparts. For patients diagnosed in 2000 to 2002, five-year relative survival was 76.2% in Ireland compared to a EUROCARE-4 mean of 79.0%, and approximately 10% below countries such as Finland, Sweden and Switzerland.[20] However, trend analysis of EUROCARE data since 1991 indicates that variation in breast cancer survival in Europe appears to be decreasing. [20;21] Differences between countries occur for a variety of reasons including timely diagnosis and treatment, and access to effective treatments.

2.4 Risk levels

Other than genetic or familial risk, there is a range of factors associated with female breast cancer, the most important of which are increasing age and lifetime exposure to oestrogen.[5;22] Risk is increased by early menarche, late menopause, and obesity in postmenopausal women. It is also modified by childbirth: nulliparity[±] and low parity are associated with an increase in risk as is late age of first pregnancy; breastfeeding appears to have a protective effect. Use of oral contraceptives and hormone replacement therapy cause a small increase in breast-cancer risk, while use of anti-oestrogenic drugs in women at high risk of breast cancer reduces risk.

[±] The condition of not bearing children.

Women with a personal history of breast cancer have an increased risk of developing a second primary tumour in the contra-lateral breast compared to those without such a history. Risk appears increased in women with a history of certain types of benign breast disease and those of a higher socio-economic status. Alcohol, smoking and exposure to ionising radiation appear to increase risk while increased physical activity appears protective.[23;24]

Breast cancer is a predominantly sporadic disease, with approximately 25% of all cases related to familial or hereditary risk. Hereditary breast cancers are often characterised by mutations associated with a high probability of cancer development (i.e., a high penetrance genotype), vertical transmission through the mother or father, early age of onset, high incidence of bilateral disease and association with other tumours. In contrast, familial breast cancers generally do not exhibit the same inheritance patterns or onset age. These cancers may be due to genetic mutations associated with a lower probability of cancer development (low penetrance genes), a chance clustering of sporadic cases or due to a shared environment.

An estimated 30% of cases associated with familial or hereditary risk can be attributed to a number of identified high penetrance genes such as *BRCA1*, *BRCA2*, and *TP53*. Mutations in the *BRCA1* and *BRCA2* genes are rare in most populations (with an estimated prevalence between 0.12% to 0.3%).[25;26] Some population groups have a higher incidence of *BRCA* mutations. For example, 2.0%–2.5% of Jewish women of Ashkenazi descent are carriers.[25]

The *BRCA1* and *BRCA2* germline mutations confer a lifelong risk of breast cancer of up to 60% to 80% depending on the screened population. *BRCA1* and *BRCA2* mutation carriers frequently develop breast cancer at a younger age, with much of this risk occurring between 30 and 50 years.[27] Genetic factors are also thought to contribute to 25% to 35% of cases diagnosed before the age of 30 years.[6] The probability of developing breast cancer in 10-year age bands by risk category has been estimated previously (Table 2.2).[28]

Table 2.2 Ten-year probability of developing breast cancer by risk category[28]

Age	Probability (%) of breast cancer diagnosis in next 10 years				
	Relatives with breast cancer			Mutation	
	None	One first degree	Two first degree	*BRCA1*	*BRCA2*
20	0.04	0.1	0.2	1.8	1.0
30	0.4	1.0	2.0	10.0	6.6
40	1.4	2.5	5.2	20.0	15.0

The incidence of breast cancer increases with age (Table 2.3) with incidence in the *BRCA1* and *BRCA2* populations being much higher than in the general population.

Table 2.3 Cancer incidence (%) by age and *BRCA* mutation[29]

Age	*BRCA1*	*BRCA2*	General population*
20-24	0.02	0.02	0.00
25-29	0.11	0.12	0.01
30-34	0.74	0.36	0.02
35-39	1.59	0.78	0.06
40-44	2.92	0.91	0.13
45-49	4.28	1.34	0.20

* *General population estimates based on National Cancer Registry Ireland data 2007-2009.*

Risk classifications for female breast cancer have been set out by the National Institute for Health and Care Excellence (NICE) in the UK.[7] This classification system has been recommended by the National Cancer Screening Service (NCSS) Expert Group on Hereditary Cancer Risk for adoption in Ireland.[3] Women are classified as average, moderate or high risk based on their 10-year risk between ages 40 and 50 or their lifetime risk, of developing breast cancer (Table 2.4). Risks are calculated using a combination of data from Claus et al.[30] and the Collaborative Group on Hormonal Factors in Breast Cancer.[31]

Table 2.4 Risk classifications for women with an elevated risk of breast cancer

Average Risk	Moderate risk	High risk
A 10-year risk of less than 3% between age 40 and 50 years and a lifetime risk of less than 17%.	A 3% to 8% risk of developing breast cancer between age 40 and 50 years or a lifetime risk of ≥17% but < 30%	A greater than 8% risk of developing breast cancer between age 40 and 50 years or a lifetime risk of greater than 30%.

Estimating the number of women in each risk category in Ireland is complicated by a lack of evidence regarding prevalence. There is no national registry of women with relevant genetic mutations.[32] International data suggest that approximately 25% of breast cancer incidence is due to familial risk.[5] It is generally assumed that 5% to 10% of cancer incidence is attributable to genetic factors, half of which is in *BRCA1* and *BRCA2* mutation carriers.[33] In a Dutch study the relative contribution to incidence of *BRCA1* and *BRCA2* was in the ratio of 4:1,[34] although this ratio is subject to substantial variability. An Irish study reported an incidence ratio of 4:5 for *BRCA1*:*BRCA2* breast cancer patients.[32] By using the estimated proportions of cancers attributable to each level of risk in combination with the reported probabilities of breast cancer and observed incidence, it is possible to estimate the

approximate numbers of women in each risk category (Table 2.5). The estimates of population in each risk group are based on the proportions outlined above which are often based on small study populations. It is assumed that those proportions will be broadly applicable to the Irish population. The majority of the population are at average risk, with an incidence of 54.9 per 100,000 in the 20-49 age group. For moderate and high risk groups, the equivalent incidence is 107.0 and 306.7 per 100,000 respectively.

Table 2.5 Estimated national population and annual incidence in each risk category and age group

Age group	Risk category					
	Average		Moderate		High	
	Population	Incidence	Population	Incidence	Population	Incidence
20 - 24	156,815	1	9,717	0	3,178	1
25 - 29	166,963	8	10,346	2	3,387	3
30 - 34	158,633	33	9,829	5	3,214	6
35 - 39	146,846	79	9,099	10	2,976	12
40 - 44	137,973	167	8,549	19	2,799	20
45 - 49	126,370	243	7,830	24	2,565	24

In Ireland, the percentage of women less than 50 years in the average, moderate and high risk groups is estimated to be 92.4%, 5.7% and 1.9%, respectively. A previous study estimated the percentage population in the average, moderate and high risk groups to be 92.7%, 6.9% and 0.4%, respectively.[35] A high risk population of only 0.4% is likely to be an underestimate given the suggestion that 1% of women have a genetic predisposition and would probably be considered high risk.[36] In women aged less than 50 years, the percentage incidence of breast cancer in the average, moderate and high risk groups is 80.8%, 9.2% and 10.0%, respectively. There is a disproportionate burden of breast cancer in the high risk group, as only 2% of the population has 10% of incidence. The figures presented here are an approximation only and form the basis for estimating the relative proportions in each risk group. It should also be noted that the known population in the high and moderate risk groups is only a small portion of the true population in those risk groups, which has yet to be fully quantified.

2.5 Key Messages

- Breast cancer is the most common invasive cancer in women in Ireland, accounting for 32% of all cases of invasive cancer and 16% of female cancer-related deaths.
- Twenty-five percent of diagnoses are in women aged less than 50 years, with 10% of deaths, an average of 88 deaths per annum between 2005 and 2010, occurring in this age group.
- Regardless of age, prognosis is strongly linked to stage of diagnosis, with five-year survival probability of 98.9% for those diagnosed at stage I compared to 27.7% when diagnosed at stage IV.
- Although breast cancer is a predominantly sporadic disease, 25% of cases relate to familial risk with 5% to 10% of all cases related to genetic predisposition.
- The 10-year risk of breast cancer between ages 40-50 years is less than 3%, between 3% and 8% and greater than 8% for women classified as being at average, moderate and high risk of breast cancer, respectively.
- The percentage of Irish women less than 50 years in the average, moderate and high risk groups is estimated to be 92.4%, 5.7% and 1.9%, respectively.
- Women at high risk of breast cancer contribute disproportionately to the incidence of early breast cancer. Although comprising less than 2% of the population, women at high risk are estimated to contribute 10% of incidence of breast cancer in women aged less than 50 years.

3 Technology description

A number of potential diagnostic tests can be performed as part of a breast cancer surveillance programme to monitor individuals known to be at an increased risk of breast cancer. These include film and digital mammography, magnetic resonance imaging (MRI), ultrasound and clinical breast examination (CBE). The purpose of this chapter is to describe the two technologies, digital mammography and MRI, that were within the scope of this HTA.

3.1 Introduction

The technology being assessed is surveillance of women under the age of 50 at an elevated risk of breast cancer using digital mammography, MRI, or a combination of the two. MRI and digital mammography are both imaging techniques that can identify breast cancers. Surveillance, as opposed to screening, refers to monitoring individuals known to be at an increased risk of disease. Surveillance is a secondary preventive measure that aims to detect breast cancer at the earliest possible stage. In contrast, primary preventive measures (e.g., prophylactic mastectomy) aim to prevent development of a malignancy in the first place.

3.2 MRI

3.2.1 Description of MRI

MRI is a high-resolution anatomical imaging technique that uses a strong external magnetic field to produce images of biological tissues. A rapidly fluctuating magnetic field, with a typical strength of 1.5-3.0 Tesla, is generated that acts on hydrogen protons in body tissues. Receiver coils measure the radiofrequency pulse generated. The signals produced vary according to the local chemical, structural and magnetic environment, thus providing a contrast between the different tissue types.

MRI of the breast is used for the detection and characterisation of breast disease. When using an MRI machine that is fitted with a dedicated breast coil, multiple cross-sectional images of the breast are generated that may be viewed in three dimensions (side-to-side, top-to-bottom, front-to-back). Administration of an intravenous gadolinium-based contrast agent is required to differentiate between normal breast tissue and benign or malignant breast lesions.

Unlike mammography, MRI does not involve exposure to ionising radiation. It has been reported that the sensitivity of MRI is not affected by breast tissue density to the same extent as mammography.[37-39] However, hormonal factors such as menopausal status, use of hormone replacement therapy and phase of menstrual

cycle have been shown to affect breast parenchymal enhancement. For this reason, it is recommended that MRI surveillance in pre-menopausal women is performed in the second week of the menstrual cycle, when background parenchymal enhancement is lowest.[40] Surveillance MRI is usually deferred in women who are lactating as efficacy in cancer detection is reduced.[41]

MRI is contraindicated in patients with ferromagnetic implants (e.g. intracranial ferromagnetic aneurysm clips, intraocular ferromagnetic foreign bodies), electronic implants that are incompatible with exposure to magnetic fields (e.g. cardiac pacemakers, automatic cardiac defibrillators, implanted neurostimulators, cochlear implants). Use of gadolinium is contra-indicated in pregnancy, end-stage renal disease, acute renal injury, haemodialysis, and where there is a history of hypersensitivity to gadolinium chelates.

3.2.2 Process

MRI is widely available in acute hospitals in the publicly funded healthcare system, although there are reports of significant capacity issues that limit access. Breast MRI is not directly available through BreastCheck (the national population-based breast screening programme for women aged from 50 to 64 years) as it is not used for screening purposes in this setting; access is purchased through the acute hospitals or through private services as necessary. Of note, it is recommended that breast MRI should only be offered by institutions that can also offer MRI-guided biopsy or that are in close contact with a site that can perform this procedure for them.[40] Currently, access to MRI-guided breast biopsies is limited to four of the eight regional cancer centres in Ireland, all in Dublin.

Breast MRI is performed using an MRI machine fitted with a dedicated breast coil. A radiographer with specialised training in breast MRI is required for set-up and scanning. The patient is placed lying prone with the breast positioned in the dedicated breast coil. Images are acquired before, during and after bolus intravenous administration of a gadolinium-based contrast agent. The examination takes approximately 30 minutes. Resulting images are read by trained breast radiologists. Suspicious lesions are evaluated based on their morphology as well as their contrast uptake and washout enhancement characteristics.

Women who suffer from claustrophobia may find the confined space of the MRI machine difficult and so refuse surveillance, but this is rare.[42] An oral anxiolytic may be offered prior to the procedure if necessary. Allergy to gadolinium, the intravenous contrast agent is reported to be very rare, with moderate to severe reactions observed in approximately 2 in 10,000 patients in a large series of over 50,000 patients.[43] Obesity and body habitus can also be an issue in MRI imaging: table

weight limits range from 160-190Kg while there is a gantry limit of approximately 60 cm in diameter. These limits may prevent some patients from fitting in the unit.[44]

The use of MRI in a breast cancer surveillance programme needs to take place within a wider quality assurance framework that adheres to relevant standards for audit, training, safety and best clinical practice.[45] Such a framework would be required should a decision be made to develop a national MRI-based surveillance programme for women at elevated risk of breast cancer.

3.3 Digital mammography

3.3.1 Description of Digital Mammography

A mammogram is an X-ray of the breast that is used in breast cancer detection. Mammography is based on the principle of differential absorption of X-rays between the various tissue components of the breast such as fat, fibroglandular tissue, tumour tissue and calcifications, with fat being more radiolucent (blacker in the image) than the other tissues (which are 'denser' or whiter in the image). The density of a mammogram is therefore determined by the relationship between fat and fibroglandular tissue; the denser the mammogram, the more fibroglandular tissue present. In full-field digital mammography, the image receptor used in film screen mammography is replaced by a digital detector; in all other respects, the imaging techniques are the same. The use of digital mammography allows the image acquisition, processing and image display to be physically and operationally separated. The images obtained are stored through a picture archiving and communication system (PACS), thereby enabling remote assessment and interpretation in addition to allowing manipulation of the retrieved image to improve visualisation.

Dense breast tissue is associated with a decrease in the sensitivity of mammography reducing efficacy in cancer detection.[46] Screening and surveillance mammography are usually deferred for this reason in women who are pregnant or lactating.[41]

3.3.2 Process

In Ireland, digital mammography is the primary breast imaging modality for screening asymptomatic women aged 50 to 64 years. It is also used for the investigation of symptomatic women and for the follow up of women with a previous history of breast cancer. It is provided in the publicly funded healthcare system through two main routes: BreastCheck – the national population-based breast screening programme for women aged from 50 to 64 years; and through the eight regional cancer centres and three regional hospitals for women who present

symptomatically or who do not otherwise meet the criteria for the BreastCheck programme.

A screening mammogram consists of four low-dose X-rays, two per breast. The breast is compressed to a firm, but tolerable level between two plates. Cranio-caudal and mediolateral oblique views are obtained as standard. Compression is required to ensure that a good quality mammogram is obtained. It helps to eliminate motion artefacts and improves visualisation by reducing superimposition of structures. Compression also reduces the radiation dose by reducing breast thickness and improves image contrast by increasing the proximity of the breast to the detector. Although compression is reported as uncomfortable by some women, it has been reported to be better tolerated if its importance is explained. Imaging is completed by a radiographer and typically takes 15 minutes. All images are viewed immediately by the radiographer prior to concluding the examination. Images are then sent for radiology assessment, picture archiving and communication.[47;48]

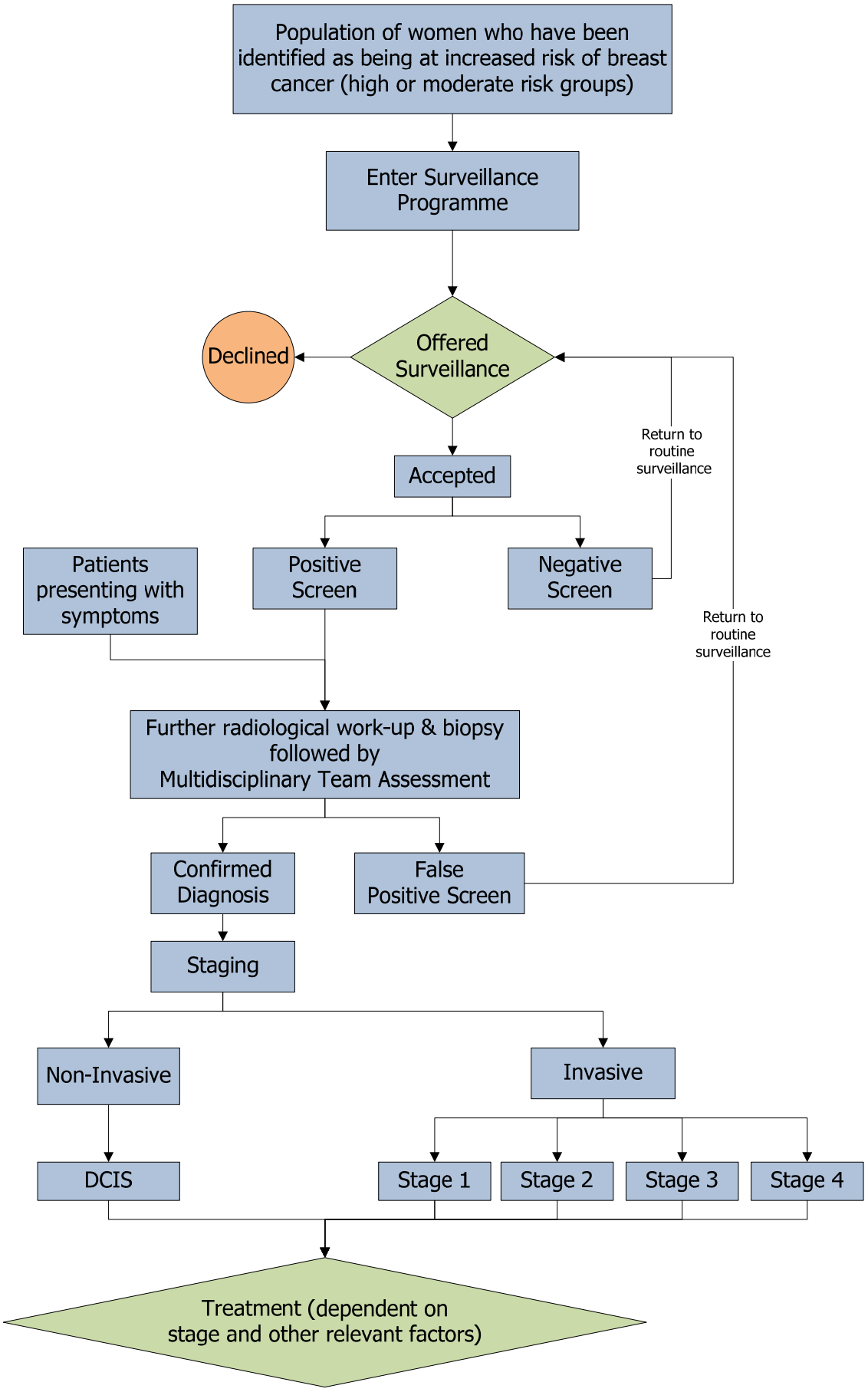
Diagnostic mammograms differ from screening mammograms in that the former are used to evaluate a patient with a positive clinical finding, such as a breast lump or an abnormal screening mammogram. In a diagnostic mammogram, additional views, such as spot compression or magnification views are taken to investigate the finding in question.[49]

Detailed national quality assurance guidance for the medical, diagnostic and technical aspects of breast screening has been available in Ireland since 2000 and was last updated in 2008. These high-level standards aim to deliver a safe and effective service and are in line with international guidelines to ensure that the best service is provided to women.[3] The quality assurance guidance details the required training, standards and continuous professional development to which all members of the breast screening programme must adhere.

3.4 Description of the surveillance process

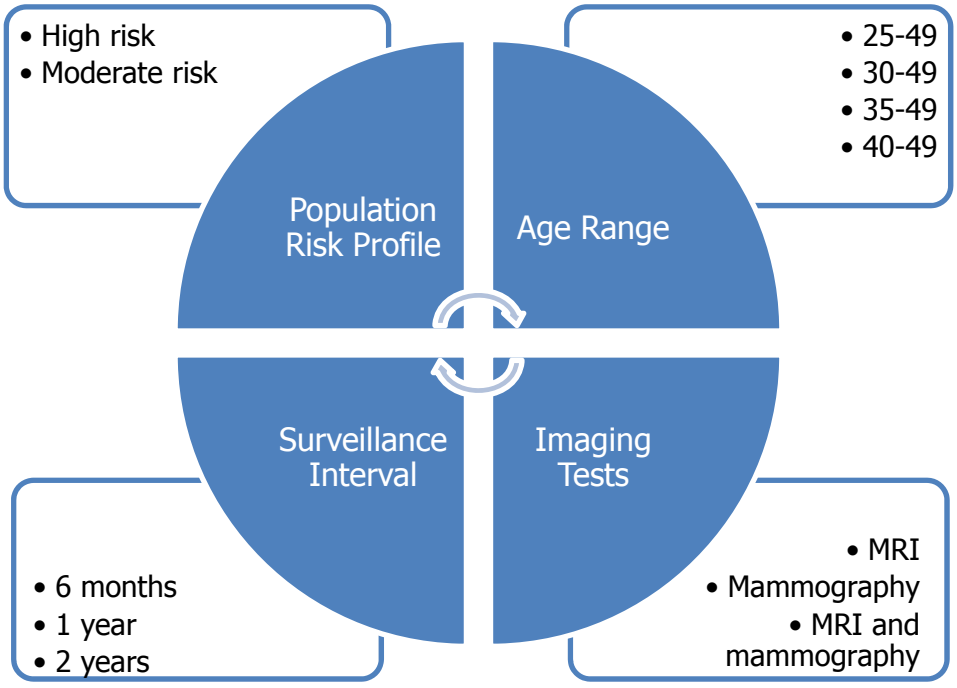
A flow chart showing the different stages in a surveillance programme is shown in Figure 3.1.

Figure 3.1 Surveillance flow chart



Women who have been identified as being at elevated risk of breast cancer are invited to participate in a surveillance programme that may consist of mammography, MRI or a combination of both at certain intervals. The overall clinical outcomes of a surveillance programme will depend on the choice of population (age range and risk profile), imaging modality and testing interval. Different combinations of risk groups, age ranges, imaging modalities and surveillance intervals that could be used in a prospective surveillance programme are shown in Figure 3.2.

Figure 3.2 Components of a surveillance programme and list of potential options within each component



A summary of the role of MRI and mammography in clinical guideline recommendations and surveillance programmes that are currently in place in a number of other countries is provided in Table 3.1.

Table 3.1 International surveillance programmes and clinical guideline recommendations

	Risk profile	Age Range	MRI	FMX/ DMX	Inter-val	Literature sources
UK						
NHSBSP[50]	Family history	40-49	No	Yes	1 year	Leach[42]
	TP53 (Li-Fraumeni)	20-29	Yes	No	1 year	
		30-39	Yes	No	1 year	
		40-49	Yes	Yes	1-year	
		50+	Maybe*	Yes	1 year	
	BRCA1, *BRCA2,* or not tested, but equivalent high risk	20-29	No	No	NA	
		30-39	Yes	No	1 year	
		40-49	Yes	Yes	1 year	
		50+	Maybe*	Yes	1 year	
Canada						
Ontario[51]	Family history or genetic mutation	30 - 69	Yes	Yes	1 year	N/A
Alberta[52]	Strong family history or genetic mutation	25-69	Yes	Yes	1 year	NHCTF[53] NICE[7] NCCN[54] CCO[55] ACS[56]
Holland[57]	*BRCA1* / *BRCA2*	25-30	Yes	No	1 year	N/A
		30+	Yes	Yes	1 year	
Australia						
DoHWA[58]	1/8 > Lifetime risk < 1/4	40+	No	Yes	1 year	ACS[56] Hadden[59] Krieg[60] Boetes[61] Warner[62] Kuhl[63] Leach[42] Lehman[64]
	1/4 > Lifetime risk < 1/2	40+	Yes	Yes	1 year	
USA						
NCCN[49]	5-Year risk ≥ 1.7%	35+	No	Yes	1 year	ACS[56], Warner[62] Leach[42] Stoutjesdijk[65] Kuhl[63] (see guideline)
	Lifetime risk ≥ 20%	30+	Maybe	Yes	1 year	
	Strong family history or genetic mutation	25+	Yes	Yes	1 year	
ACS[56]	Family history or genetic mutation (lifetime risk~20-25%)	30+	Yes	Yes	1 year	Kriege[60] Kuhl[63] Leach[42] Lehman[64] Warner[62] (see guideline)
Europe						
ESMO[5]	*BRCA1* / *BRCA2*	25+	Yes	Yes	1 year	Kriege[60]

Key: NHSBSP – National Health Service Breast Screening Service; DoHWA – Department of Health, Western Australia; NCCN – National Comprehensive Cancer Network, USA; ACS – American Cancer Society; ESMO – European Society for Medical Oncology; NHCTF – National Hereditary Cancer Task Group; NICE – National Institute for Health and Care Excellence; CCO – Cancer Care Ontario.

** Requirement for MRI to be reviewed annually on basis of background density.*

The evidence underpinning these surveillance recommendations is noted to be limited in a number of these guidelines with recommendations based on non-randomised screening trials and observational studies or expert consensus opinion. Most surveillance programmes limit use of mammography to those aged 30 years and older because of an unfavourable risk-benefit profile in younger women. The use of MRI is discussed as an adjunct to mammography to address the potential limitations of mammography surveillance in younger women (reduced test sensitivity in dense breasts and exposure to ionising radiation) with none of these guidelines addressing the potential use of MRI as a sole surveillance strategy. The UK guidelines have been undergoing a process of review over the last three years and were put out to public consultation in January 2013.[66] The main revisions have been to state that, other than for research purposes, women aged less than 40 at elevated risk of developing breast cancer should not have any mammography surveillance and only digital mammography should be used for those aged 40 to 49. Furthermore, for women with *TP53* mutations, no mammography surveillance should be used before the age of 50.

The age ranges and surveillance intervals in this HTA were chosen based on the review of research evidence, a review of surveillance programmes elsewhere and through discussion with the Expert Advisory Group. All possible permutations were not assessed as some potential combinations of the above parameters did not represent feasible surveillance strategies due to clinical, logistical or resource requirements. For instance a biennial programme that alternates between MRI and mammography in the 45-49 year age group would not represent a feasible option due to the relatively short period of time between entering and leaving the programme. Potential surveillance programmes that were included are shown in Table 3.2.

The surveillance scenarios modelled in this evaluation are described in more detail in Chapter 5 (Economic Analysis).

Table 3.2 Surveillance options: potential imaging modalities, surveillance intervals and age ranges

Surveillance programme	Description	Population (age and risk profile)
Biannual alternating DMX/MRI	Women will alternate between receiving a mammogram or MRI scan every six months	Each of these potential surveillance programmes will be modelled separately for sub-groups within the high-risk cohort; the high risk; and the moderate risk group within each of the following age bands: • 25-49 years • 30-49 years • 35-49 years • 40-49 years.
Annual DMX	Mammogram every year	
Annual MRI	MRI scan every year	
Annual DMX+MRI	Mammogram and MRI performed at the same time every year	
Annual alternating DMX/MRI	Women will alternate between receiving a mammogram or MRI scan every year	
Biennial DMX	Mammogram every two years	
Biennial MRI	MRI scan every two years	
Biennial DMX+MRI	Mammogram and MRI scan performed at the same time every two years	

Key: DMX – digital mammography; MRI – magnetic resonance imaging.

Mammography and MRI images are classified according to the Royal College of Radiologists Breast Group (RCRBG) imaging classification system.[67] This system specifies five different categories (1-5) with a prefix indicating which imaging modality was used (MRI for MRI and M for mammography). Table 3.3 provides a description of each of the five categories, along with a summary of how these relate to the American College of Radiology BI-RADS classification system, which was the system used in the studies included in the review of the sensitivity and specificity of mammography and MRI for this HTA.

Table 3.3 Comparison of BI-RADS and RCRBG imaging classification systems (adapted from Maxwell et al. 2009[67])

Category	BI-RADS	RCRBG
0	Assessment incomplete. *Need to review prior studies and/or complete additional imaging*	-
1	Negative. *Continue routine screening*	Normal/no significant abnormality. *There is no significant imaging abnormality*
2	Benign finding. *Continue routine screening*	Benign findings. *The imaging findings are benign.*
3	Probably benign finding. *(<2% chance of malignancy) Short-term follow-up mammogram at 6 months, then every 6-12 months for 1-2 years*	Indeterminate/probably benign findings. *There is a small risk of malignancy. Further investigation is indicated.**
4	Suspicious abnormality. *Perform biopsy, preferably needle biopsy*	Findings suspicious of malignancy. *There is a moderate risk of malignancy. Further investigation is indicated.*
5	Highly suspicious of malignancy: appropriate action should be taken. *Biopsy and treatment, as necessary*	Findings highly suspicious of malignancy. *There is a high risk of malignancy. Further investigation is indicated.*
6	Known biopsy-proven malignancy, treatment pending. *Assure that treatment is completed*	-

Key: BI-RADS – American College of Radiology Breast Imaging Reporting and Data System; RCRBG – Royal College of Radiologists Breast Group.

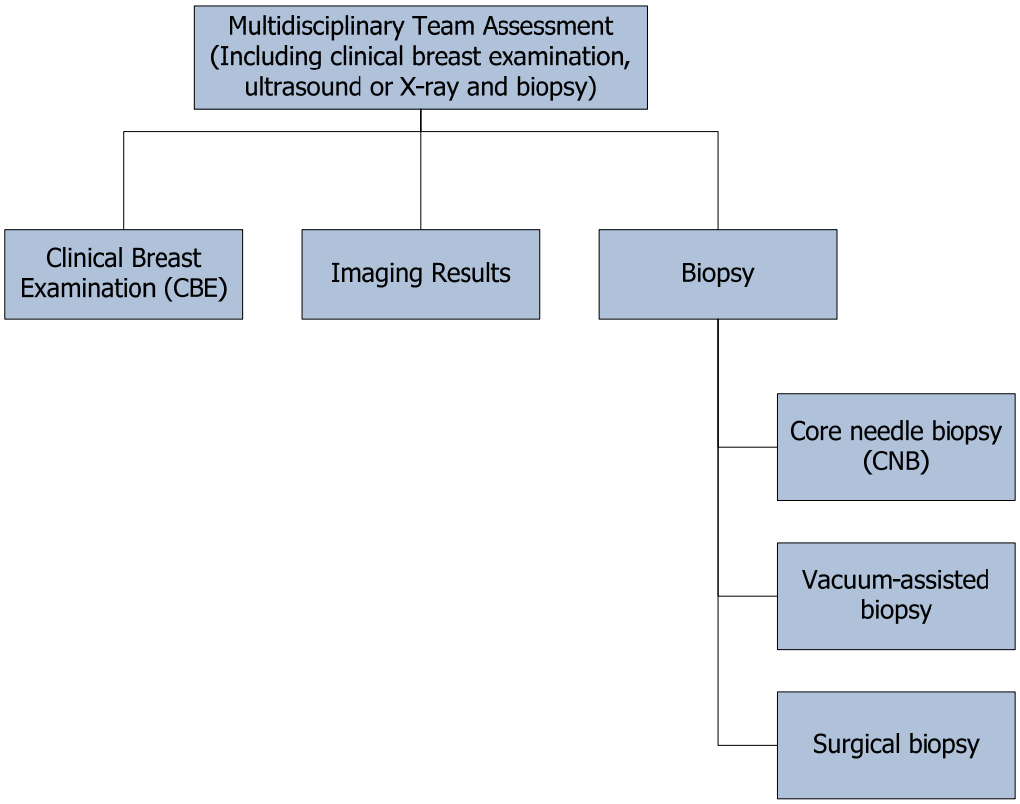
* *No short interval follow-up recommended in RCBRBG system.*

Women with negative screens remain in the surveillance programme and undergo repeat imaging at the next surveillance interval. Women who are symptomatic are referred directly to a symptomatic breast clinic for triple assessment.[≠] Asymptomatic women with an abnormal test result are recalled to the radiological assessment clinic. The aim of this assessment is to establish a diagnosis of malignant or benign pathology so that further treatment can be planned or the woman returned to routine surveillance. It is assumed that women within the surveillance programme who present symptomatically between surveillance intervals will also be assessed at the radiological assessment clinic. Clinics are attended by a breast radiologist trained and experienced in breast screening, nursing staff, appropriate radiography staff and supported by clerical staff. The assessment process involves further imaging

[≠] An assessment which includes clinical examination, imaging and pathology tests.

(ultrasound and supplementary mammographic views), as necessary, clinical examination and biopsy for histology where indicated. Image-guided (MR-, ultrasound- and stereotactic-guided) biopsy is used as appropriate. In suspected cases of cancer, ultrasound of the axilla is also performed to determine if there are lymph node abnormalities, with image-guided biopsy of suspicious nodes performed for further assessment as necessary. The results of all assessments that include a biopsy are discussed at the weekly multidisciplinary team meeting (Figure 3.3).

Figure 3.3 Multidisciplinary assessment of positive surveillance test result



If the results of the multidisciplinary assessment indicate that the surveillance test result was a false positive, the patient remains in the surveillance programme and receives another imaging procedure at the next surveillance interval. Patients with a confirmed diagnosis of breast cancer will undergo further tests to determine the stage of their cancer. Appropriate treatment will be provided based on cancer stage and other relevant clinical information. Treatment options include wide local excision, mastectomy, sentinel node biopsy and axillary node dissection, radiotherapy, hormone therapy and chemotherapy. (See Table 5.2 in Chapter 5, Economic Evaluation.)

3.5 Key Messages

- Unlike mammography, there is no radiation exposure associated with MRI. However, MRI requires the administration of a contrast agent prior to imaging.
- The sensitivity of mammography is lower for women with dense breast tissue. Tissue density is less of a factor in MRI surveillance.
- Due to the potential for hormonal factors to influence the performance of MRI, diagnostic accuracy may be higher if testing is performed in week two of the menstrual cycle.
- It is recommended that surveillance MRI is deferred in pregnancy and lactation as the gadolinium-based contrast agent is contraindicated in pregnancy.
- There are a range of age groups, imaging modalities and surveillance intervals that could potentially be employed in a surveillance programme. International practice varies, however, current guidance typically avoids use of mammography in those aged less than 30 years and limits use of surveillance MRI to that of an adjunct to mammography.

4 Summary of clinical effectiveness and safety

A range of diagnostic tests can be performed as part of a breast cancer surveillance programme. These include film and digital mammography, magnetic resonance imaging (MRI), ultrasound and clinical breast examination (CBE). In line with the agreed scope of the HTA, the review of clinical effectiveness and diagnostic accuracy will focus on digital mammography and MRI. The first part of this chapter deals with a review of the evidence of the diagnostic accuracy of these two imaging modalities in women with an elevated risk of breast cancer. This is followed by a brief summary of the literature in regard to the overall effectiveness of breast cancer surveillance programmes. The expected impact of introducing surveillance in Ireland is not based on this review of clinical effectiveness; rather estimates of the sensitivity and specificity of MRI, digital mammography and a combination of MRI plus digital mammography will be combined with other relevant clinical data to model the expected effect of introducing a surveillance programme in Ireland.

4.1 Diagnostic accuracy of MRI and mammography

4.1.1 Search strategy

A systematic review of the literature was carried out to examine the diagnostic accuracy of mammography, MRI and a combination of mammography and MRI, in women at elevated risk of breast cancer. This section outlines the methods used to identify relevant studies, assess methodological quality and extract data. Results from each of the included studies are provided along with a narrative summary and a meta-analysis of the pooled data. Finally a discussion of the results is provided, which includes a description of the limitations of the data and the implications these may have in interpreting the results.

A search for studies comparing MRI, mammography and a combination of MRI and mammography was carried out in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and the Health Technology Assessment Database were also searched for relevant secondary studies. Reference lists from reviews were searched to identify primary studies. Full details of the search are provided in Appendix 1. The PICO (Population, Intervention, Comparator, Outcomes) analysis used to formulate the search is presented in Table 4.1.

Table 4.1 PICO analysis for identification of relevant studies

Population	Women under 65 years at an elevated risk of breast cancer through either genetic factors and/or family history
Intervention	Surveillance for breast cancer using MRI, film or digital mammography, or MRI plus film or digital mammography
Comparator	MRI, film or digital mammography or MRI plus film or digital mammography
Outcomes	Sensitivity and specificity

A study participant age limit of 50 years was not applied to the search despite being specified in the terms of reference for this HTA, since scoping searches indicated that there is insufficient evidence available for this age group. Instead the age limit was increased to 65 years in order to capture the best available information with regard to the comparative sensitivity and specificity of each surveillance test in a cohort of younger women at elevated risk of breast cancer. Similarly, to ensure that relevant results would not be excluded, a specific risk classification system was not used as an exclusion criterion. Instead an elevated risk category based on genetic profile and family history was sufficient for inclusion as long as the patient selection criteria used in the study were reported clearly. Results were reviewed according to the inclusion criteria by two researchers independently and any disagreements were resolved through discussion. The methodological quality of included studies was performed in Review Manager[68] using the abbreviated QUADAS tool developed by the Cochrane Diagnostic Test Accuracy Working Group.[69] Data extraction was performed independently by two researchers, with incomplete data extraction and, or disagreements being resolved through discussion. As the results of the search revealed a lack of studies comparing digital mammography and MRI specifically, a subsequent search for studies comparing digital and film mammography in a general population of women aged less than 50 years was carried out in MEDLINE and Embase using keywords specific to these two screening modalities. Data extraction from selected studies was again carried out independently by two researchers.

4.1.2 Results

Five studies[42;46;62;63;70] comparing surveillance with MRI to surveillance with mammography in women less than 65 years of age at elevated risk of breast cancer were identified; three[42;46;63] of these also provided data for surveillance using a combination of MRI and mammography. All of these studies used film mammography, except for one,[70] which used a mixture of film (45%) and digital (55%) mammography. No studies exclusively comparing MRI with digital mammography in this population were identified. A narrative summary of these studies is provided below. Sensitivity and specificity data from these studies for MRI, mammography and the two combined are shown in Tables 4.3, 4.4 and 4.5,

respectively. Table 4.2 provides data on the country where the study was carried out, number of participants involved, frequency of surveillance and average size of invasive tumours identified by each imaging method. A list of studies that examined breast cancer surveillance in high risk women that did not meet the criteria for inclusion is provided in Appendix 2, along with the reason for their exclusion.

Table 4.2 Summary of study details and results from all included studies

Study name	Country	N	Imaging modality	Frequency of screening	Follow-up	Sensitivity	Specificity	Tumour size (mm)
Kriege 2006[46]	Netherlands	1365	FMX	Annual	1-4 years	0.36 [0.20, 0.55]	0.95 [0.94, 0.96]	N/R
			MRI			0.70 [0.51, 0.84]	0.89 [0.88, 0.90]	N/R
Kuhl 2005[63]	Germany	529	FMX & DMX	Annual	2-7 years	0.33 [0.19, 0.49]	0.97 [0.96, 0.98]	13.2 (SD 7.8)
			MRI			0.91 [0.78, 0.97]	0.97 [0.96, 0.98]	12.4 (SD 6.7)
Leach 2005[42]	United Kingdom	649	FMX	Annual	2-7 years	0.40 [0.24, 0.58]	0.93 [0.92, 0.95]	14.7 (SD 10.2)
			MRI			0.77 [0.60, 0.90]	0.81 [0.80, 0.83]	16.0 (SD 8.2)
Warner 2004[62]	Canada	236	FMX	Annual	1-3 years	0.36 [0.17, 0.59]	1.00 [0.99, 1.00]	12.4 (SD 4.6)
			MRI			0.77 [0.55, 0.92]	0.95 [0.93, 0.97]	10.8 (SD 5.2)
Sardanelli 2011[70]	Italy	501*	FMX & DMX	Annual	1-4 years	45.5 [24.4, 67.8]	98.7 [97.5, 99.5]	N/R
			MRI			88.9 [65.3, 98.6]	96.6 [94.8, 97.9]	N/R

Key: N – number of participants; FMX – film mammography; DMX – digital mammography; Sn – sensitivity; Sp – specificity; Tumour size – average size of screen detected invasive tumours in millimetres; SD – standard deviation; N/R – not reported.
** Figure relates to women of all ages as not reported separately for women aged less than 50 years.*

The MRISC study[46] by Kriege et al. is a non-randomised, prospective, multicentre cohort study in which 1,909 women with a cumulative lifetime risk of breast cancer greater than 15% underwent surveillance every six months by clinical breast exam and annually by mammography and MRI. Risk classification was performed according to the modified tables of Claus et al.[34;71] and the overall study population included women aged 25 to 70 years of age. Nineteen percent of participants had a confirmed *BRCA1* or *BRCA2* mutation. Sensitivity and specificity results were provided by menopausal status; results for postmenopausal women are excluded in this review on the assumption that they are not representative of the target population. A total of 1,365 women were classified as premenopausal in the study. Mammography (oblique and cranio-caudal views and, if necessary, compression views or

magnification) and MRI (dynamic breast MRI with gadolinium-containing contrast medium) were performed annually, with both tests being carried out either on the same day or between day 5 and day 15 of the menstrual cycle. Results were scored using the BI-RADS[72] classification, with BI-RADS 0,3,4 or 5 being defined as a positive result. False-negative results were recorded when cancer was detected in the interval or by one of the other methods (clinical breast examination [CBE], mammography or MRI).

Kuhl et al.[63] conducted a prospective non-randomised cohort study to compare mammography, ultrasound and MRI in the surveillance of 529 women aged between 27 and 59 years with a lifetime risk of breast cancer of at least 20%. Eight percent of participants had a confirmed *BRCA1* or *BRCA2* mutation. Risk classification was defined by the Consortium on Familial Breast and Ovarian Cancer of the German Cancer Aid.[73] Film-screen mammography (medio-lateral and cranio-caudal views, additional views and spot compression if required) and MRI (dynamic axial contrast-enhanced subtracted breast MRI of both entire breasts) were performed annually. Individual tests were carried out within eight weeks of each other. Results were scored using the BI-RADS[72] classification. No BI-RADS score of 0 was recorded since women who had incomplete assessments had the entire diagnostic work-up repeated. A positive test result was defined as BI-RADS 4 or 5; BI-RADS scores of 1, 2 and 3 were considered negative. False negatives were recorded by the diagnosis of interval cancers or by confirmed positive results on another test.

The MARIBS study[42] by Leach et al. was a prospective, non-randomised cohort study that recruited 649 women aged between 35 and 49 years with a strong family history of breast cancer or a high probability (>60%) of a *BRCA1*, *BRCA2* or *TP53* mutation. Eighteen percent of participants had a confirmed *BRCA1* or *BRCA2* mutation. All women were offered annual dynamic contrast-enhanced MRI and two-view or one-view mammography. In 76% of cases, mammograms were performed on the same day as the MRI examination and in 4% of cases, they were performed over a month apart. BI-RADS[72] scores of 0, 3, 4 or 5 were classed as positive index test results. False negatives were recorded as interval cancers found during follow-up or biopsy-confirmed cancers detected by another screening test.

Warner et al.[62] carried out a prospective, non-randomised, single-centre cohort study comparing the sensitivity and specificity of MRI, ultrasound, mammography and clinical breast examination in women aged between 26 and 65 years, with a confirmed *BRCA1* or *BRCA2* mutation. The population did not include women who were at an increased risk of breast cancer through family history alone. Four-view surveillance mammograms and contrast enhanced bilateral MRI were performed on the same day. False negatives were calculated through the monitoring of interval cancers over the three-year-follow-up period and through biopsy-confirmed cancers

detected using other test methods. Test results were scored using the BI-RADS[72] classification, with a positive result being a BI-RADS score of 4 or 5.

Sardanelli et al.[70] conducted a non-randomised multi-centre trial involving 501 women enrolled between June 2000 and Jan 2007 across 18 centres in 14 towns in Italy. The study population consisted of asymptomatic women aged between 22 and 79 at high risk for breast cancer, selected for being (a) proven carriers of deleterious *BRCA1* or *BRCA2* mutations or untested first-degree relatives of *BRCA1* or *BRCA2* mutation carriers (i.e., 50% risk to be a carrier), or (b) having a strong family history of breast or ovarian cancer with three or more events in first- or second-degree relatives. Results for participants under 50 years of age were reported separately and only these are included in this meta-analysis. Surveillance consisted of annual CBE, mammography, ultrasonography and MRI for at least two screening rounds. A mixture of film screen (45%) and two types of digital mammography (28% phosphor plates digital mammography, 27% full-field digital mammography) was used. Test results were scored using the BI-RADS[72] classification, with a positive result being a BI-RADS score of 4 or 5.

Table 4.3 Diagnostic test accuracy of MRI in women aged less than 65 years at elevated risk of breast cancer

MRI							
Study	**TP**	**FP**	**FN**	**TN**	**Positive test**	**Sensitivity**	**Specificity**
Kriege 2006[46]	23	328	10	2,747	BI-RADS 0, 3, 4 and 5	0.70 [0.51, 0.84]	0.89 [0.88, 0.90]
Kuhl 2005[63]	39	39	4	1,370	BI-RADS 4 and 5	0.91 [0.78, 0.97]	0.97 [0.96, 0.98]
Leach 2005[42]	27	344	8	1,502	BI-RADS 0, 3, 4 and 5	0.77 [0.60, 0.90]	0.81 [0.80, 0.83]
Warner 2004[62]	17	20	5	415	BI-RADS 4 and 5	0.77 [0.55, 0.92]	0.95 [0.93, 0.97]
Sardanelli 2011[70]	16	21	2	595	BI-RADS 4 and 5	0.89 [0.65, 0.99]	0.97 [0.95, 0.98]

Key: MRI – magnetic resonance imaging; TP – true positive; FP – false positive; FN – false negative; TN – true negative.

Table 4.4 Diagnostic test accuracy of mammography in women aged less than 65 years at elevated risk of breast cancer

Mammography							
Study	**TP**	**FP**	**FN**	**TN**	**Positive test**	**Sensitivity**	**Specificity**
Kriege 2006[46]	12	155	21	2,920	BI-RADS 0, 3, 4 and 5	0.36 [0.20, 0.55]	0.95 [0.94, 0.96]
Kuhl 2005[63]	14	45	29	1,364	BI-RADS 4 and 5	0.33 [0.19, 0.49]	0.97 [0.96, 0.98]
Leach 2005[42]	14	121	21	1,725	BI-RADS 0, 3, 4 and 5	0.40 [0.24, 0.58]	0.93 [0.92, 0.95]
Warner 2004[62]	8	1	14	434	BI-RADS 4 and 5	0.36 [0.17, 0.59]	1.00 [0.99, 1.00]
Sardanelli 2011[70]	10	8	12	628	BI-RADS 4 and 5	0.45 [0.24, 0.68]	0.99 [0.98, 0.99]

Key: TP – true positive; FP – false positive; FN – false negative; TN – true negative.

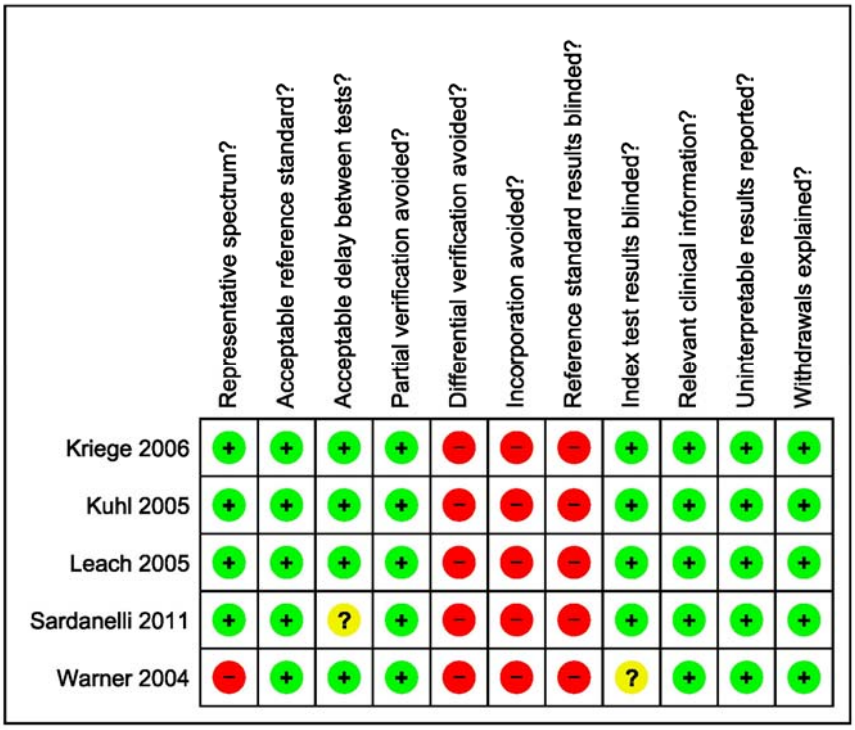
Table 4.5 Diagnostic test accuracy of combined MRI and film mammography in women aged less than 65 years at elevated risk of breast cancer

MRI and Film Mammography							
Study	**TP**	**FP**	**FN**	**TN**	**Positive test**	**Sensitivity**	**Specificity**
Kriege 2006[46]	28	456	5	2,619	BI-RADS 0, 3, 4 and 5	0.85 [0.68, 0.95]	0.85 [0.84, 0.86]
Kuhl 2005[63]	40	55	3	1,354	BI-RADS 4 and 5	0.93 [0.81, 0.99]	0.96 [0.95, 0.97]
Leach 2005[42]	33	428	2	1,418	BI-RADS 0, 3, 4 and 5	0.94 [0.81, 0.99]	0.77 [0.75, 0.79]

Key: MRI – magnetic resonance imaging; TP – true positive; FP – false positive; FN – false negative; TN – true negative.

A summary of the assessment of methodological quality of the five included studies is provided in Figure 4.1. All studies were scored as low quality on the criteria of avoiding differential verification and incorporation and for blinding of those performing the reference test. Differential verification cannot be avoided in this situation as a biopsy is only performed following a positive test. Verification of negative index test results is through the absence of interval cancers in the follow-up period (true negative) or as a biopsy confirmed positive result using a comparator index test or the presence of an interval cancer during follow-up (false negative). Similarly incorporation and blinding (of the reference test) cannot be avoided since reference tests are carried out only on foot of a positive index test result and the reference test (biopsy) relies on the index test (MRI/mammography) to identify the location of the suspicious lesion within the breast.

Figure 4.1 Methodological quality summary using the Cochrane QUADAS tool[69]



A limitation of the evidence used in this HTA was that no studies exclusively comparing MRI and digital mammography met the inclusion criteria. However two of the included studies[63;70] used a combination of film and digital mammography. Two other studies studies[74;75] were identified that involved the use of digital mammography and MRI in populations at high risk of breast cancer, but were ineligible due to an indeterminate number of the patient population being over 65 years of age.

In the first of these, Weinstein et al.[74] screened 609 women at high risk of breast cancer aged between 27 and 81 years who previously had a non-actionable film screen mammogram, using digital mammography and MRI. The comparative sensitivities and specificities are shown in Table 4.6 below.

Table 4.6 Digital mammography versus MRI in a high risk group with a non-actionable film screen mammogram – Weinstein et al[74] results

Country	N	Frequency	Follow-up	Modality	Sensitivity	Specificity
USA	609	Once off	2 years	Film screen mammography	0.33	0.94
				Digital mammography	0.39	0.91
				MRI	0.71	0.79

In the other study, Kuhl et al.[75] compared a mixture of digital and film mammography to MRI for screening in a cohort of 687 women at elevated familial risk of breast cancer aged between 25 and 71 years. Although personal correspondence with the author of this paper indicated that approximately 70% of mammograms were performed by digital mammography, individual estimates of the sensitivity and specificity of each type of mammography are unavailable. The overall results of this study are shown in Table 4.7.

Table 4.7 Mixture of digital and film mammography versus MRI in women at elevated familial risk of breast cancer – Kuhl et al.[75] results

Country	N	Frequency	Follow-Up	Modality	Sensitivity	Specificity
Germany	1679	Annual	1-3 years	Mammography (film + digital)	0.33	0.99
				MRI	0.93	0.98
				MRI + mammography	1.00	0.98

An additional search was carried out to locate studies comparing film and digital mammography in a broader population of women at average risk of breast cancer, to compare to the limited data available for populations at high risk. Two studies were identified from which all relevant data could be extracted. These were the DMIST study[76] and the OSLO II trial,[77] which in total involved over 73,000 participants, over 24,000 of whom were under 50 years of age. Pooled analysis of the sensitivity and specificity of data from women under 50 years of age from both these studies is shown in Table 4.8.

Table 4.8 Pooled sensitivity and specificity from studies[77;78] comparing film and digital mammography in women ≤50 years at average risk of breast cancer

Modality	Sensitivity	Specificity
Film mammography	0.48	0.89
Digital mammography	0.68	0.89

4.1.3 Statistical analysis

For the meta-analyses, a Bayesian bivariate, random effects approach was used.[79] The bivariate random effects model accounts for the bivariate nature of sensitivity and specificity as well as the within-study and between-study variability.[80] Analyses were carried out in R 2.14.1[81] using the bamdit package (version 1.1).[82] Four studies were available for MRI, film mammography, and the combination of MRI and film mammography. No meta-analysis of digital mammography was undertaken as only one study was available. The results of the meta-analyses are given in Table 4.9. The bounds for the estimate of specificity for digital mammography are very narrow due to the use of a single large study.

Table 4.9 Summary estimates of test sensitivity and specificity for mammography, MRI and mammography plus MRI in women aged less than 65 years at elevated risk of breast cancer

Surveillance method	Sensitivity	Specificity
MRI	0.80 (0.65-0.88)	0.92 (0.80-0.96)
Mammography	0.38 (0.26-0.51)	0.97 (0.87-0.98)
MRI and film mammography	0.88 (0.78-0.93)	0.88 (0.73-0.93)

A sensitivity analysis was carried out to determine the impact of restricting the analysis to the two studies that used BI-RADS scores of 0, 3, 4 and 5 to define a positive test result. The sensitivities of MRI, film mammography and the combination of MRI and film mammography were 0.80, 0.38 and 0.88, respectively. These represent modest changes to the estimates using all studies and, given the small numbers of positives found in studies, the credible intervals are typically wide. The specificities of MRI, film mammography and the combination of MRI and film mammography were 0.92, 0.97 and 0.88, respectively. It can be anticipated that reducing the threshold for a positive test result should improve sensitivity at the expense of reduced specificity. The result of this sensitivity analysis is consistent with this expectation; that specificity is indeed reduced, although the increase in sensitivity is negligible at best. Using the combined results of the five included studies, the prevalence of breast cancer in high risk women is approximately 5.1%.

Given this prevalence, for a cohort of 1,000 women undergoing screening the following test performance can be expected:

	MRI	Mammography
Positive predictive value (PPV)	35.3% (15.7 – 52.9%)	36.8% (12.6 – 58.3%)
Negative predictive value (NPV)	98.8% (97.8 – 99.3%)	96.6% (95.8 – 97.3%)
Likelihood ratio for positive test result (LR+)	10.13 (3.45 – 20.87)	10.86 (2.69 – 26.21)
Likelihood ratio for negative test result (LR-)	0.22 (0.12 – 0.42)	0.65 (0.51 – 0.79)

Given the relatively high MRI sensitivities reported in two of the included studies,[63;70] the meta-analysis was run with these studies excluded in order to test the impact on the sensitivity and specificity results if an assumption was made that the three remaining studies represented a more realistic expectation of how a national surveillance programme would perform in practice. The results indicate a pooled sensitivity of 74% (95% CI 55%-86%) for MRI and 39% (95% CI 22%-62%) for mammography and specificities of 88% (95% CI 69%-94%) and 94% (95% CI 57%-98%) for MRI and mammography, respectively.

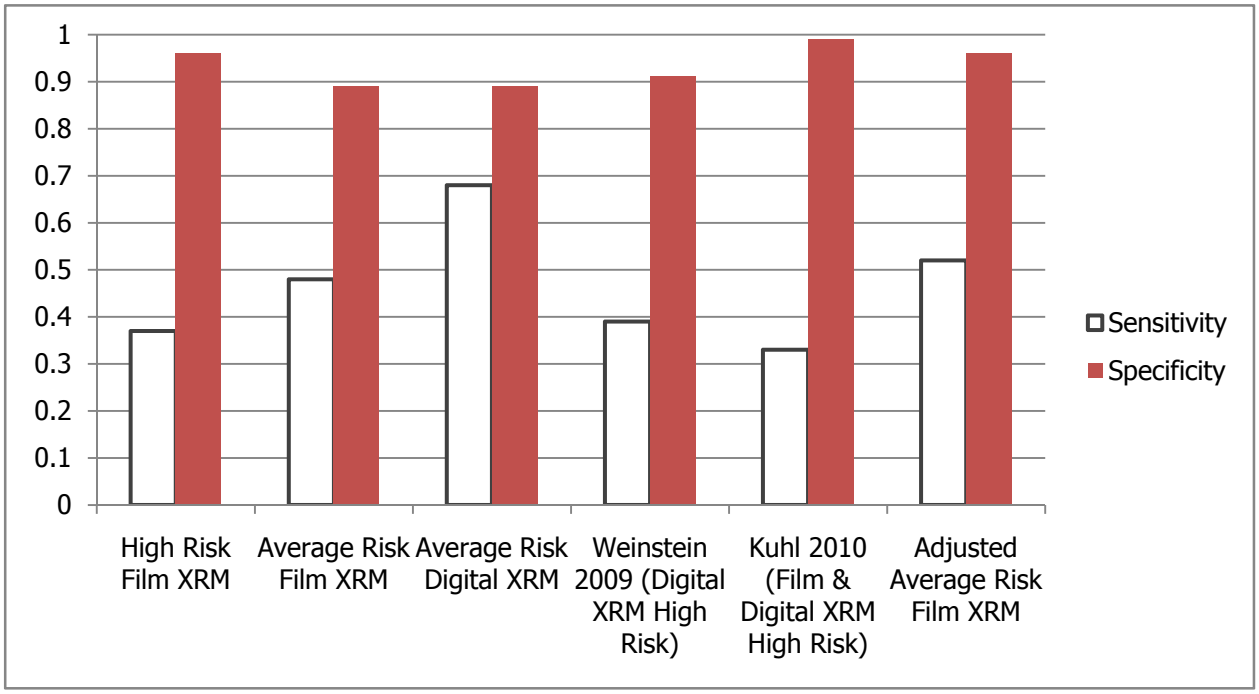
4.1.4 Discussion

A variety of limitations were encountered in regard to the comparative diagnostic test accuracy data for the population of interest in this HTA. Only one study[42] comparing surveillance with MRI and mammography only in women less than 50 years of age at elevated risk of breast cancer was identified in the literature. Increasing the age limit to 65 years resulted in five studies being included.[42;46;62;63;70] There were also differences in how a positive index test was defined between the four included studies. Two studies used a BI-RADS score of 0, 3, 4 or 5 as a positive result, with three studies only deeming BI-RADS scores of 4 or 5 to constitute a positive result. Contrary to what one would expect, the highest estimates of sensitivity come from studies that had a narrower definition of a positive test (i.e. only BI-RADS 4 and 5).

Another major limitation was the lack of data on the sensitivity and specificity of digital mammography in younger women at elevated risk, since all studies meeting the inclusion criteria involved film mammography (one being a mixture of film and digital). Two other studies that involved digital mammography in women at high risk, but not limited to under 65s indicate that the point estimate for sensitivity and specificity ranges between 33% to 39% and 91% to 99%, respectively. When data from younger cohorts of average risk women are examined, significantly higher

estimates for the sensitivity of both film and digital mammography are observed (see Figure 4.2).

Figure 4.2 Comparison of the point estimates for sensitivity and specificity for film and digital mammography in different populations (age ranges and risk groups)



The evidence base for the diagnostic accuracy of digital mammography in women at elevated risk of breast cancer is incomplete. The high sensitivity values observed in large volume screening trials in women at average risk are inconsistent with the limited data available for studies in populations at elevated risk of the disease. While younger age and increased breast tissue density negatively affect the diagnostic accuracy of mammography,[46;83-85] differences in risk profile and tumour characteristics are also likely to influence the accuracy of the test.[83] Therefore the use of data from younger populations at average risk may not offer a valid method of estimating the sensitivity of digital mammography for populations at elevated risk. A more conservative approach is to base estimates on the (predominantly) film mammography results in the target elevated-risk population on the basis that: (1) it is reasonable to assume that digital mammography will be at least as effective as film mammography; and (2) there is currently no published data to support the greater accuracy of digital mammography in this population. While there is evidence to suggest that digital mammography performs better in younger, average-risk populations,[78] it is unclear if this improvement would also extend to an elevated-risk population. This conservative approach has the advantage of at least establishing a lower bound for the diagnostic accuracy of digital mammography.

An alternative approach to estimating the diagnostic accuracy of digital mammography in the elevated risk cohort is to apply a proportionate percentage increase to the sensitivity estimate for film mammography in this cohort that is consistent with the improved accuracy seen with digital mammography in average risk women younger than 50 years. This would involve an assumption that even though populations with different risk profiles are not considered to be equivalent, the relative difference between film and digital mammography in both populations would be.

After due consideration of these issues, it was concluded that the predominantly film mammography results from studies directly comparing MRI and mammography in populations at elevated risk provide the most reliable and methodologically sound data in relation to the likely performance of digital mammography in this group. This approach is further supported by the limited amount of primary data on digital mammography in women at elevated risk of breast cancer,[74;75] which report sensitivity values that are broadly in line with the film mammography results.

Notwithstanding these limitations, the results of this review are consistent with other published reviews concerning surveillance of women at elevated risk of breast cancer,[86-88] showing MRI to have the greatest sensitivity of any single test, with a combination of MRI and mammography producing an increase in sensitivity over MRI alone, along with a slight decrease in specificity.

4.2 Clinical effectiveness of MRI and mammography

While diagnostic accuracy is an important factor in a surveillance programme, it does not provide information about how effective such a programme is likely to be in terms of clinically relevant, patient-centred outcomes. The overall effectiveness of a surveillance programme requires a broader consideration of the probability of adverse health outcomes in the absence of surveillance, the degree to which surveillance identifies all people who would suffer these adverse health outcomes and the magnitude of incremental health benefits of earlier versus later treatment resulting from surveillance.[89]

The effectiveness of surveillance of women at an elevated risk of breast cancer will be modelled in this assessment using data from a number of sources, including the incidence of cancer in this population, the accuracy of the diagnostic test and the effect of earlier versus later treatment. However to provide context, a brief summary of the reported effectiveness of screening in women with an elevated risk profile due to family history or genetic factors is provided below. This includes a summary of the reported effects of surveillance on breast cancer mortality and the potential harms associated with surveillance.

4.2.1 Mortality reduction

During this HTA, no studies were identified that estimated the reduction in relative risk of breast cancer mortality achieved by surveillance in women under 50 years of age at elevated risk of breast cancer. However there is evidence to show a mortality reduction of 15% associated with screening in average risk populations.[90] This mortality benefit has also been shown in younger cohorts of average risk women, with the relative risk of breast cancer mortality being estimated as 0.85 (95% CI: 0.75-0.96) for women aged between 40 and 49 years undergoing screening mammography.[91] However there are also a number of randomised controlled trials that have failed to show a mortality benefit in this population.[88]

The primary aim of a breast cancer surveillance programme is to reduce mortality through early detection of tumours. When detected at stage I, five-year survival rates of over 90% are achieved.[92] Digital mammography may be more sensitive, but less specific than film mammography in women aged between 40 and 49 years, and hence may lead to greater mortality reductions, but increased false positives.[93] Part of the mortality benefit in many trials for women screened in their 40s is likely due to screening performed after the age of 50.[94] A randomised controlled trial that applied an upper age limit of 48 found a relative risk of breast cancer mortality of 0.84 (95% CI: 0.66-1.04) in the screened cohort.[95] In the same trial, in order to prevent one death from breast cancer over 10 years, the number needed to invite for screening was 2,512. For an average risk population, it has been suggested that the harms may outweigh the benefits when screening in women under 50.[96;97]

MRI is only recommended for women at high risk of developing breast cancer, with mammography recommended for those at average or moderate risk of developing breast cancer.[98] Currently, there is no published evidence for a reduction in mortality associated with MRI screening.[99] Cancer detection rates are higher when MRI or a combination of MRI and mammography are used, compared to mammography alone.[86] Studies examining screening with MRI have, to date, been limited to women at high risk of breast cancer and a review in 2011 failed to find any prospective randomised trials of breast cancer screening using MRI in general or high-risk populations with survival as an endpoint.[87]

The assumption that earlier detection will result in increased survival may not apply across all subgroups within the cohort at high risk of breast cancer. Differences in the natural history of breast cancer in those with an elevated risk profile could potentially limit the effectiveness of surveillance. For women with a *BRCA* mutation, there is evidence to suggest that in addition to earlier onset, cancer is often more aggressive[100] with nodal spread not being correlated with the size of the primary tumour.[101;102] Specifically, a high portion of *BRCA1* cancers are triple negative (estrogen receptor, progesterone reception and HER2 receptor negative) and high

grade lesions. Triple negativity is documented as a strong adverse prognostic factor in early breast cancer.[103] That there are differences in the nature of the disease in different populations is supported by data from mammographic screening, which shows that women diagnosed between the ages of 20 and 39, who are more likely to have a germline mutation, have lower survival rates than older groups.[104] A study by Moller[105] found no association between pathological stage at diagnosis and survival for *BRCA1* carriers. This introduces the possibility that earlier detection can have a variable impact on clinical outcomes across different risk categories.

4.2.2 Safety

In making any surveillance decision, the benefits and risks must be considered. Apart from a reduction in breast cancer mortality, there are a variety of additional effects of surveillance or screening (Table 4.10).

Table 4.10 Non-mortality related effects of surveillance[94]

Positive effects	Negative effects
Detection of tumour at earlier stage (possibly predictive of less toxic treatment)	Radiation-induced carcinoma
Improved cosmesis	Unnecessary biopsies
Reassurance	Psychological stress of call-back
Reduced anxiety about cancer at time of screening	Additional X-ray films
	Possible false reassurance

For those who have cancer, the effects of surveillance are primarily positive. In addition to the potential improved clinical outcomes and cosmesis for those whose tumour is detected at an earlier stage, there is also the potential for increased reassurance for people with a family history of breast cancer. However, there is also a potential for adverse consequences for women who do, but especially for those who do not have breast cancer. Risks include false negatives, false-positive findings, overdiagnosis, inconvenience, pain and anxiety as well as the potential toxicity due to mammography-related radiation exposure or allergies to the contrast media required for breast MRI.

False negatives (cancer present, but test results reported as normal) can lead to false reassurance.[10] Of note, it is recognised and accepted that false negatives will occur even as part of an optimal screening or surveillance programme. The European guidelines for quality assurance in breast cancer screening and diagnosis state that false-negative cases should not exceed 20% of the total number of interval

cancers.[45] The minimum standard for interval cancers (i.e., breast cancers diagnosed in the interval between scheduled screening episodes in women screened and issued with a normal screening result) in BreastCheck is <0.75/1,000 women screened in year-one and <1.25/1000 in year-two. Therefore, an optimal surveillance programme providing a biennial surveillance programme may have a false-negative rate of up to 0.15/1000 and 0.25/1000 women screened in years one and two, respectively.[106] A delayed diagnosis of less than three months is viewed to have no clinical impact on the course of the disease.

For those who do not have cancer, there are some primarily negative effects of surveillance, particularly associated with false-positive test results and recalls. A false positive occurs when a woman who does not have cancer has an abnormal test result and is recalled for further follow-up investigations. This can lead to additional worry and distress as well as potential pain and anxiety due to additional unnecessary procedures, particularly in the use of biopsies to confirm an initial positive test result. The risk of a false positive result is strongly correlated with the recall rate. This rate is influenced by factors relating to the screening or surveillance programme (e.g., screening interval and technique, image quality, number of views, training and experience of radiologists, single versus double reading of images), whether it is an incident or prevalent screen, and characteristics of the woman being screened (age, breast density, use of hormone-replacement therapy).[107;108] The cumulative probability of a 40- to 49-year-old woman receiving at least one false-positive mammography result after 10 years is estimated at 62% with annual mammography.[88] Data from the BreastCheck programme in Ireland indicates that for women aged between 50 and 54, the overall 10-year recall rate is approximately 34%.[109] The recall rate in this programme, which involves biennial mammographic screening for women aged between 50 and 64 years of age, decreases with age, with the 10-year recall rate for the 60-64 age group dropping to approximately 30%.[109]

Large scale surveillance programmes also carry the risk of overdiagnosis, which can occur when a detected tumour lacks potential to progress to a clinical stage or when death from other causes occurs before the breast cancer surfaces clinically. In both instances, the woman would be treated with no survival benefit. Surveillance may also detect ductal carcinoma in situ (DCIS). It is not currently possible to discriminate between in situ cancers that will develop into invasive disease and those that would not progress if undetected.[14] Finding the former may extend some women's lives, but finding the latter serves only to increase the number of women who are over-diagnosed.

As noted in section 3.2, Chapter 3, use of an intravenous gadolinium-based contrast agent is required in breast MRI. Allergy to this agent is reported to be very rare, with

moderate to severe reactions observed in approximately 2 in 10,000 patients.[43] Use of gadolinium is contra-indicated in those with a history of hypersensitivity to gadolinium chelates, in pregnancy, end-stage renal disease, acute renal injury and in haemodialysis.

4.2.2.1 Radiation risk

As previously noted, MRI does not involve exposure to ionising radiation. Digital mammography is associated with a small dose of radiation to the breast. In some women at high risk of breast cancer, it is suggested that there is an increased sensitivity to the DNA-damaging effects of ionising radiation.[110] Frequent exposure of breast tissue to radiation doses from a young age (such as in a surveillance programme) may carry a risk of breast cancer induction. This excess risk decreases exponentially as a function of increasing age, such that below age 30, there may be a higher rate of causing cancer with screening mammography than of detecting early-stage cancer.[98] A 2010 review of radiation risk for women at high risk for breast cancer concluded that annual mammography for women aged 30 years or older who carry a breast cancer susceptibility gene or who have a strong family history of breast cancer has a favourable benefit-risk ratio, with an estimated one additional cancer induced for every 16 to 18 detected. For women aged less than 30 years an unfavourable benefit-risk ratio was found due to the challenges of detecting breast cancer in younger women, the aggressiveness of cancers at this age, the potential for radiation susceptibility at younger ages and a greater cumulative radiation exposure.[111] This finding is supported by a large European study published in 2012 among *BRCA1* and *BRCA2* mutation carriers, which found that exposure to any ionising radiation before age 30 was associated with an increased risk of breast cancer (hazard ratio 1.90, 95%CI: 1.20-3.00); this risk was dose-related. This increased risk was seen at doses substantially lower than those shown to be problematic in other cohorts exposed to ionising radiation emphasising the potential increased radiosensitivity of *BRCA* mutation carriers.[112]

The risk of death from radiation-induced cancer has been estimated as 8 per 100,000 women screened annually for 10 years beginning at age 40.[94] For *BRCA1* and *BRCA2* mutation carriers, the proportion of diagnosed cancers attributable to radiation exposure has been estimated at less than 2% and less than 4%, respectively.[113]

The effects of surveillance will be considered in greater detail in Chapter 5, which will describe the model that will be used to estimate the potential benefits and harms associated with a surveillance programme for women aged less than 50 years of age at elevated risk of breast cancer, and provide a rationale for the various clinical and economic parameters included.

4.3 Key Messages

- There is limited evidence directly comparing surveillance MRI, film mammography and digital mammography in women less than 50 years at elevated risk of breast cancer.
- The estimated sensitivity and specificity of MRI for the target population are 0.80 and 0.92, respectively.
- The estimated sensitivity and specificity of digital mammography for the target population are 0.38 and 0.97, respectively. These estimates are mainly based on film mammography data due to the lack of studies comparing digital mammography and MRI only in women at elevated risk of breast cancer.
- The estimated sensitivity and specificity of combined MRI and digital mammography for the target population are 0.88 and 0.88, respectively.
- The overall effectiveness of a surveillance programme for women at elevated risk of breast cancer depends on the combination of age range, imaging modality and surveillance interval used.
- There is a lack of mortality data on surveillance in women under 50 at elevated risk of breast cancer. However, there is evidence of a mortality reduction in average risk populations through earlier detection and treatment.
- Surveillance has non-mortality effects that are both positive (e.g., early detection leading to improved survival) and negative (e.g., radiation-induced carcinoma, overdiagnosis and unnecessary biopsies). The ratio of benefits to harms depends on the target population.
- Frequent exposure to radiation through a mammography-based surveillance programme from a young age may increase the risk of developing breast cancer.

5 Economic evaluation

As determined in the review of clinical effectiveness, breast cancer screening in older women at average risk of breast cancer has been shown to reduce breast cancer mortality compared to no screening. It is assumed that such benefits will also be observed in a surveillance programme of a population of younger women at elevated risk of developing breast cancer. The purpose of this section is to:

- examine previously published economic analyses of surveillance of women at elevated risk of developing breast cancer
- develop an economic model for breast cancer surveillance of women less than 50 years of age in Ireland at elevated risk.

5.1 Review of published literature

A systematic review of the cost-effectiveness of breast cancer surveillance in women aged less than 50 years at elevated risk of breast cancer was conducted. Detailed descriptions of the literature search terms, inclusion and exclusion criteria, data extraction methods and study characteristics are provided in Appendix 2. To supplement this, a review of published HTAs relating to surveillance in women at elevated risk of breast cancer was undertaken. The purpose of these reviews was to identify and evaluate the methodological and modelling methods used by other groups, to assess their relevance, and to provide context for this assessment.

In the systematic review of the cost-effectiveness literature, seven economic evaluations, five from the US[114-118] and two from the UK,[119;120] published between 2006 and 2011 were considered relevant. The included studies are detailed in Table 5.1. Costs included in the table were inflated to 2011 and converted to euro for the purpose of this review.

Table 5.1 Studies included in systematic review of cost-effectiveness analyses of breast cancer surveillance in women at an elevated risk of developing breast cancer

Study	Setting	Risk group	Screen modality and comparator	Model approach	Outcomes assessed	Discount rate	Costs included	Incremental cost-effectiveness ratios*
Griebsch et al. (2006)[119]	UK NHS	*BRCA1/2*, *TP53* carriers, their close relatives and others of high familial risk.	Annual MRI and XM+MRI vs XM, aged 35-49.	Trial based analysis	Cancers detected	3.5	Screening costs	All risk groups: MRI dominated; XM+MRI €66,100/cancer; *BRCA1*: MRI €27,300/cancer; *BRCA2*: MRI dominated; XM+MRI €35,800/cancer.
Taneja et al. (2009)[118]	US	*BRCA1/2* and ≥ 20% cumulative lifetime risk.	Annual XM, MRI and XM+MRI vs. XM at age 40 (1 screening event only)	Not described	QALYs	3	Screening, diagnostics and treatment	*BRCA1/2*: MRI dominated; XM+MRI €33,200/QALY. ≥20% risk: €59,900 - €409,300/QALY.
Moore et al. (2009)[116]	US	Women with ≥ 15% cumulative lifetime risk.	Annual MRI vs XM from age 25-50.	Markov cohort	QALYs	5	Screening, diagnostics and treatment	MRI €225,600/QALY.
Lee et al. (2010)[115]	US	*BRCA1*	Annual XM, MRI, XM + MRI from age 25 vs no screening.	Probabilistic Markov	QALYs	3	Screening, diagnostics, treatment and patient time.	XM €20,400/QALY; MRI dominated; XM+MRI €83,900/QALY.
Norman et al. (2007)[120]	UK NHS	*BRCA1* carriers 30-39 and 40-49	Annual XM, MRI, XM + MRI for 10 years starting between 30-39 and 40-49 vs no screening.	Markov cohort	QALYs	3.5	Screening, diagnostics and treatment	40-49: XM €5,600/QALY; MRI dominated; XM+MRI €15,100/QALY. 30-39: XM €10,100/QALY; MRI dominated; XM+MRI €26,200/QALY.
Grann et al. (2011)[114]	US	*BRCA1/2*	Annual XM, XM+MRI from age 30, prophylactic mastectomy, prophylactic oophorectomy and chemoprevention.	Probabilistic Markov	QALYs	3	Screening, diagnostics and treatment plus indirect costs	*BRCA1*: XM+MRI €123,900/QALY. *BRCA2*: XM+MRI €71,900/QALY.
Plevritis et al. (2006)[117]	US	*BRCA1/2*	Annual XM, XM+MRI from 25 to 69 with alternative start and stop ages at five-year intervals vs no screening.	Probabilistic Markov in continuous time	QALYs	3	Screening, diagnostics, treatment and lost productivity	*BRCA1* 40-49: XM+MRI €57,200/QALY; *BRCA1* 25-69: XM+MRI €625,300/QALY; *BRCA2* 40-49: XM+MRI €146,600/QALY; *BRCA2* 25-69: XM+MRI €961,200/QALY.

** All costs inflated to 2011 and converted to €.*

There was considerable variation between the economic evaluations in terms of the risk subgroups analysed, the surveillance strategies compared and the model design.[114-120] Sensitivity analyses conducted in the reviewed studies suggest the three main drivers of cost-effectiveness were: MRI cost,[114-119] breast cancer risk[114;115;117;118] and test sensitivity.[115-118]

In all seven studies, the cost of MRI was considerably higher than the cost of mammography ranging from a 7-fold[120] to 19-fold[116] difference. The difference in cost between the two technologies in Ireland is considerably smaller, with the cost of an MRI estimated to be approximately 2.5 times that of a mammogram. Thus, the ICERs (incremental cost-effectiveness ratios) reported for MRI in the reviewed studies are higher (that is, less cost-effective) than would be expected in this assessment.

Three of the US studies assessed annual imaging from a relatively young age (25 years) [115-117] until the late 60s or older. Consequently, the relatively high ICERs (lower cost-effectiveness) of adding MRI to mammography from the US studies may, in part, be a consequence of the early starting ages of the surveillance programmes. Plevritis et al.[117] considered a range of ages over which MRI might be added to mammography and noted that adding MRI to mammography over the 40-49 age range was more cost-effective than adding MRI over a range of 25-69.

All the reviewed studies assessed film rather than digital mammography. Norman et al.[120] noted that digital mammography can have markedly higher sensitivity than conventional film mammography, citing sensitivities of 51% and 78% for screen and digital mammography, respectively. Given the sensitivity of cost-effectiveness to test sensitivity, the cost-effectiveness estimates for mammography alone from the reviewed literature are likely to be inferior to what could be achieved with digital mammography.

Of the seven studies reviewed, six were model-based analyses, five of which were Markov models[114-117;120] with one unspecified model type.[118] The complexity of the models varied between studies. For example, some models differentiated disease by tumour size,[114;115;117;118] grade[114;117] and lymph node involvement,[114;116;118] while others did not disaggregate disease stages. Other areas of methodological variation included the estimation of the reduction in mortality from screening and handling of competing risk of other cause mortality. It is unclear, however, if more detailed models generated more accurate estimates of cost-effectiveness.

To supplement this systematic review, a review of published HTAs was undertaken. A detailed description of the literature search terms and a summary of the studies identified is provided Section 2, Appendix 2. Seven reports were identified; all targeted surveillance in those at high risk of breast cancer, with two specifically

assessing surveillance in those with a known genetic predisposition. Variable definitions of risk were used. The technologies compared varied, with MRI assessed either in combination with, or as an alternative to, mammography; one HTA comparing digital to film mammography was included for completeness. Six of the HTAs were published between 2004 and 2007 and thus were completed prior to the availability of some of the more recent research results that are included in this analysis. Only one HTA comparing MRI and mammography-based surveillance that included limited economic modelling is directly relevant. Published by the Medical Services Advisory Committee, Australia, in 2006, it concluded that MRI in combination with mammography may be cost-effective for surveillance of female carriers of a *BRCA1* mutation aged 35-54, but was unlikely to be cost-effective for those at lower risk.

In summary, the published literature provides limited and inconsistent evidence regarding the cost-effectiveness of surveillance for women aged less than 50 years at elevated risk of breast cancer. Given the substantial difference between some of the key parameters influencing the results of the cost-effectiveness studies and those used in this assessment, the conclusions from any of these studies are unlikely to generalise to the Irish context.

In Ireland, there is no fixed threshold above or below which technologies are guaranteed to be rejected or accepted for reimbursement. Although consideration of the cost-effectiveness of a technology is necessary, it must be noted that it is not the sole basis for decision making with other factors including affordability (as addressed by budget impact), feasibility and equity issues impacting on decisions. Economic evaluations of other interventions that have been adopted in Ireland following a determination that they were cost-effective include population-based colorectal cancer screening[121] (€1,696/QALY); universal Human Papillomavirus vaccination for 12-years-olds[122] (€17,383/LYG); universal infant pneumococcal conjugate vaccination[123] (€5,997/LYG) and universal infant hepatitis B vaccination[124] (€37,018/LYG). Historically, the probability of a drug being considered cost-effective at a threshold of €20,000/QALY and €45,000/QALY has been included as a reference point in pharmacoeconomic evaluations undertaken to inform decisions regarding the reimbursement of drugs on the HSE community drugs scheme.

5.2 Description of the economic model

Economic modelling facilitates the combination of data on costs and benefits from different sources and allows these to be extrapolated into the future. Breast cancer surveillance incurs ongoing running costs, while any benefits (e.g. QALYs) may extend over many years. Modelling allows the short-term nature of some costs to be offset against the long-term nature of any health benefits in the economic evaluation.

The budget impact analysis (BIA) provides a means to predict the potential financial impact of introducing breast cancer surveillance into the healthcare system. Whereas an economic evaluation addresses the additional health benefit gained from investment in a technology, BIA addresses the affordability of the technology (e.g. the net annual financial cost of adopting the technology for a finite number of years).

5.2.1 Study question

What is the cost-effectiveness and budget impact of a range of surveillance options for women aged less than 50 years at elevated risk of developing breast cancer? The surveillance options included digital mammography, MRI or a combination thereof at different surveillance frequencies and starting ages.

5.2.2 Type of economic evaluation

As there is a meaningful difference in terms of important patient outcomes between the technologies being compared, this evaluation used a cost-utility analysis (CUA), with the outcomes expressed in terms of quality-adjusted life years (QALYs). Additional outcomes such as breast cancer mortality at age 50 are also presented.

5.2.3 Study perspective

Costs were assessed from the perspective of the publicly funded health and social care system in Ireland. Following the national guidelines[125] only direct medical costs (i.e. fixed and variable medical costs associated with the provision of a technology) were included. Indirect costs, such as decreased productivity due to disease or death, or out-of-pocket expenses incurred by individuals attending for a surveillance or diagnostic test were excluded.

5.2.4 Technology

The technology being assessed was breast cancer surveillance using either digital mammography, MRI, or a combination of the two.

5.2.5 Choice of comparators

The comparators were no surveillance, and the existing system of 'no organised surveillance', that is where limited surveillance is provided on an ad hoc basis. The existing surveillance for women at elevated risk is ill-defined. It was assumed that women with known high penetrance genetic mutations currently receive MRI surveillance in line with the 2006 NICE guidelines:[7] women with *BRCA1* and *BRCA2* mutations and other identified mutations other than *TP53* receive annual MRI from age 30, and women with a *TP53* mutation receive annual MRI from age 20. It was assumed that these women also receive digital mammography surveillance from age 30 or 35. The 2006 NICE guidelines recommend the addition of digital mammography from the age of 40.

Based on a review of a local hospital database the following definition was used to describe the existing ad hoc surveillance for women at high familial risk: from the age of 30, 85% annual surveillance, 11% biennial surveillance and 4% no surveillance. For women at moderate risk the following surveillance was assumed: from the age of 30, 70% annual surveillance, 24% biennial surveillance and 6% no surveillance. It was assumed that only digital mammography is used for surveillance in women at high familial and moderate risk. These data are only an approximation of existing ad hoc surveillance and are used to estimate current budget impact.

A number of women classified as average risk are currently also receiving surveillance. There are a number of possible reasons for this, such as risk factors not recorded in the available data or as a result of patient request. Ad hoc surveillance for presenting women classified as average risk comprises: 37% annual surveillance, 42% biennial surveillance, and 21% no surveillance. Only digital mammography is currently used for women in this risk group.

5.2.6 Target population

The target population for this assessment was women aged less than 50 years of age who are classified as being at elevated risk of developing breast cancer due to either a genetic predisposition or a strong family history. No central register is available of women by risk group. The known population was estimated using a variety of data sources including the National Centre for Medical Genetics, family risk clinics and international prevalence studies (Table 5.2). The estimates were then validated using expert opinion. By applying the assumptions about current surveillance to the estimated population, the calculated number of annual surveillance mammograms is broadly comparable with the figure recently estimated by the National Cancer Control Programme (NCCP),[126] and independently collected data from 11 publicly funded hospitals. The figures presented in Table 5.2 represent the number of women by risk group that were receiving surveillance or who are

otherwise known to the family risk clinics, at the time of this HTA. It does not represent the actual population at elevated risk of breast cancer, as there are many women at elevated risk, but not currently identified as such (see Table 2.5).

Table 5.2 Estimated population of women in Ireland aged less than 50 years by risk group receiving surveillance or otherwise known to the family risk clinics during this HTA

Risk group	Known population less than 50 Median	(95% CI)
BRCA1	160	(87 to 237)
BRCA2	117	(52 to 198)
Other high penetrance genetic mutations	80	(63 to 99)
High familial risk	1,674	(1,241 to 2,326)
Moderate risk	2,456	(1,725 to 3,650)

Although the known population is a small proportion of the estimated total population in Ireland, capacity constraints on the family risk clinics and genetic testing will likely prevent a significant increase in the identified population in the short to medium term.

It was also estimated that 2,376 (95% CI: 1,654 to 3,496) women classified (appropriately or otherwise) as average risk are currently presenting at family risk clinics, with a large proportion receiving some form of surveillance.

5.2.7 Time horizon

The model followed a hypothetical cohort of 1,000 women from age 20 to life expectancy for women at age 50. The costs and benefits relating to outcomes were estimated to patient life-expectancy.

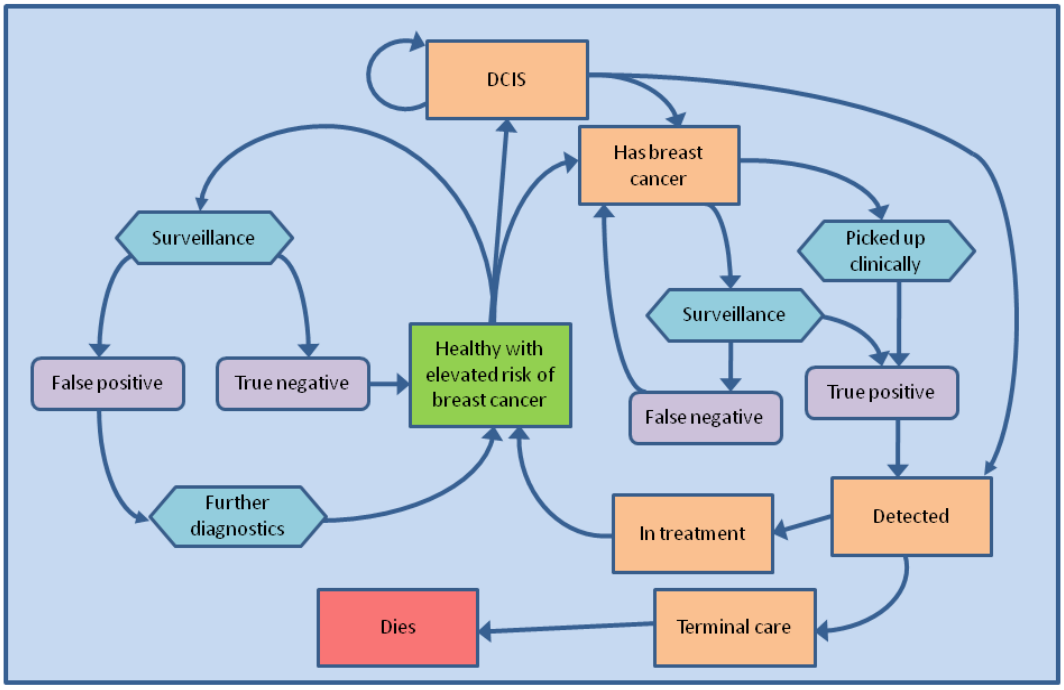
5.2.8 Outline of the model structure

A Markov model structure was used for the economic evaluation in this HTA. In a Markov model it is assumed that a patient is always in one of a finite number of distinct health states. All events are represented as transitions between states with transition probabilities dictating the likelihood of moving from one state to another.

In this model, an individual woman was modelled from age 20 using consecutive six-month cycles. At the end of each cycle the woman was in one of 10 mutually exclusive states: healthy; undetected DCIS; undetected invasive cancer at six months, 12 months, 18 months and 24 months, respectively; detected cancer; in treatment; terminal breast cancer; or deceased. Death occurred automatically when a woman reached life expectancy specific to the age at which surveillance ceases

(that is, for a woman at age 50, life expectancy is 83[127]). During any cycle a woman could transition from any state to the deceased state due to other causes (i.e. all cause mortality). The results for 1,000 women were aggregated to generate cohort level results.

Figure 5.1 Schematic of Markov model



Note: in any cycle of the model a woman can transition from any state to the deceased state due to all-cause mortality.

The model was adapted from a spreadsheet-based model developed by Norman et al. for estimating the cost-utility of MRI surveillance for women with *BRCA1* mutations.[120] The model was adapted to enable greater flexibility in setting surveillance strategies in terms of start age and frequency. The model was also expanded to include more data specific to stage at diagnosis, such as treatment, QALYs, and survival. The model was developed as a fully probabilistic model allowing all of the key parameters to vary in each simulation. The model was written in the statistical programming language R.[81] Where model results were summarised across cohorts, a median outcome is reported. In all cases a mean was also evaluated and results were checked for consistency of interpretation whether a mean or median was used for summarising outcomes of interest.

For the CUA, individual women were simulated from age 20 with the assumption that all start in the healthy state (i.e. none of the women have cancer at the outset). Simulation was repeated for 75,000 women and then estimates for a cohort of 1,000 women were generated by sampling with replacement from the 75,000 simulations. Sampling was repeated 5,000 times to generate distributions for the outcomes of

interest. In phase one of the evaluation, strategies were applied only for a five-year age band (or 10 years, in the case of 40-49 year olds). The purpose was to determine plausible start ages for surveillance and whether any strategies may be dominated by (found to be more expensive, but less effective than) no surveillance for a particular age group. In phase two, selected full strategies were tested (using the relevant start ages from phase one); these could have increasing frequency and intensity of surveillance for successive age groups.

For the BIA, it was assumed that surveillance would be applied to the known population who would not all be the same age and could be in any of the health states other than deceased. The ages of the women in the cohort at the start of the BIA were sampled from family risk clinic data for the relevant risk subgroup. The health states for a risk subgroup were sampled using the health status data generated in the CUA model for ad hoc surveillance for the equivalent risk subgroup, as this should be reflective of the health states of women undergoing surveillance at present.

5.2.9 Surveillance strategies

Strategies for surveillance were defined by the imaging method, start age and frequency. Imaging methods were digital mammography; MRI; and a combination of the two. The starting ages used were 25, 30, 35 and 40 years. The frequencies tested were every 6, 12 and 24 months. For the subgroup of women with high penetrance genetic mutations other than *BRCA1* and *BRCA2*, a start age of 20 was also modelled in line with 2006 NICE guidelines for women who are *TP53* mutation carriers.[7]

5.2.10 Sensitivity analysis

A probabilistic model was used that explicitly took into account the uncertainty of the model parameters. As part of the model evaluation, all of the key parameters were varied within plausible ranges that were derived from published evidence and advice from the Expert Advisory Group. As the structure of the economic model presented here is inherently stochastic, the outputs are equivalent to a multivariate probabilistic sensitivity analysis.

The choices for two inputs to the model, the diagnostic test accuracy of digital mammography and the proportion of patients receiving each type of treatment by stage at diagnosis, were identified as being open to debate. For each of these parameters, an additional scenario analysis was undertaken using alternative inputs suggested by the EAG.

A univariate sensitivity analysis shows how influential each parameter is and how sensitive the results are to fluctuations in each parameter. Given the uncertainty around the parameters themselves, it is important to understand how this translates into uncertainty about the results. Each parameter in turn is fixed at its upper and lower bounds while all the other parameters are varied as per the fully probabilistic model. The variance in results due to each parameter can be displayed as a tornado plot. Univariate sensitivity analyses were applied for a sample of surveillance strategies to determine the influence of different parameters.

5.2.11 Budget impact analysis

The budget impact analysis (BIA) was conducted from the perspective of the publicly funded health and social care system and reports the costs for each year in which they occur, in this case for a timeframe of five years. The timeframe represents the most immediate planning horizon over which resource use will be planned. The cost data for the BIA were the same as those used in the economic analysis with the difference being that prices are inclusive of VAT, and no discounting is applied. VAT applies to non-oral medications and to equipment when calculating amortised capital costs. In this study, VAT was applied to the cost of intravenous chemotherapy, non-oral supportive medications and the costs of diagnostic imaging.

Whereas the cost-utility analysis simulated women from age 20 to life expectancy, the BIA followed the known cohort for five years. The age distribution of the known cohort was estimated from family risk clinic data. To reflect what is likely to happen in practice, a number of additional parameters were included in the BIA, which are detailed in Section 5.3. The results of the BIA are reported as the predicted five-year cost of a surveillance programme for women in each elevated risk subgroup. The estimated total numbers of digital mammograms, MRIs and MR-guided biopsies over five years are also reported.

5.2.12 Criteria for selecting recommended strategies

In the presence of two comparators (no surveillance and current ad hoc surveillance), there was a need for clear criteria for determining which surveillance strategies may be preferable. In an economic evaluation, it is common to calculate the incremental cost-effectiveness ratio compared to routine practice. A frontier can be constructed of the most efficient strategies (i.e., for a given level of cost, has the maximum effect); only strategies on that frontier and with an ICER less than some specified threshold are considered. In the context of two comparators, the situation is more complex, as surveillance strategies could be cost-effective compared to one and not the other.

A surveillance strategy was considered as preferable if:

- It was at least as effective and no more costly than existing surveillance.
- It was on, or close to the cost-effectiveness frontier when compared to a strategy of no surveillance.
- It showed a mortality reduction relative to no surveillance.

For each risk subgroup, a cost-effectiveness and budget impact analysis was performed as outlined above. The results of these analyses were then interpreted within the context of these criteria and an optimal strategy recommended for each risk subgroup.

5.3 Model parameters

The economic model required a range of input parameters that describe the diagnostic test accuracy of the imaging modalities, the probability of developing breast cancer, the types of treatment given to identified cases of breast cancer and the associated costs of surveillance, further testing and treatment. The purpose of this section is to provide details on the values used for the key parameters. As the model was probabilistic, parameters generally have a base-case value and an associated range or distribution of values.

5.3.1 Discount rate

Discounting is a technique that allows comparison between costs and benefits that occur at different times. It reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Costs and benefits were discounted at the rate of 4% as prescribed in Irish guidelines.[125] The discount rate was not varied in the analysis.

5.3.2 Diagnostic test accuracy

Data from the clinical effectiveness review in chapter 4 were used to define the diagnostic test accuracy of digital mammography and MRI (Table 5.3). Due to the lack of evidence on the diagnostic test accuracy of digital mammography in women aged less than 50 at elevated risk of developing breast cancer, the data for film mammography were used. This is a conservative approach as it is possible that digital mammography offers improved test sensitivity. The data available are all based on annual screening strategies. The Breast Cancer Surveillance Consortium (BCSC) collects data on screening mammograms from 243 facilities across the US.[128] Evidence from the BCSC suggest that the test sensitivity of digital mammography in women aged less than 50 at average risk increases with longer intervals between screens, while specificity remains unchanged. It was assumed that

sensitivity increases by 0% to 10% when the screening frequency reduces from annual to biennial. No reduction in sensitivity was applied for biannual surveillance strategies as no evidence was available to determine the possible impact on test sensitivity. The bivariate distribution of sensitivity and specificity for digital mammography and MRI were taken from the posterior distributions generated by the meta-analysis described in Section 3.1.3.

Table 5.3 Diagnostic test accuracy of digital mammography and MRI

Imaging method	Biannual and annual		Biennial
	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Sensitivity, % (95% CI)
DMX	38 (26-51)	97 (87-98)	43 (30-57)
MRI	80 (65-88)	92 (80-96)	85 (69-95)
Combined DMX and MRI	88 (78-93)	88 (73-93)	91 (82-97)

Key: DMX – digital mammography; MRI – magnetic resonance imaging; CI – confidence interval.

5.3.3 Safety

Exposure to ionising radiation increases the risk for cancer occurrence, which is of particular relevance for any surveillance strategy involving repeat attendance for mammograms. Models have been developed previously to determine the excess relative risk attributable to radiation exposure.[129] Models are based on attained-age and age-at-exposure, the latter modelling cumulative exposure. Both models have been used in a comparative effectiveness analysis of breast cancer screening strategies and produced comparable increases in risk.[113] For this study the attained-age model was used, described by the following formula:

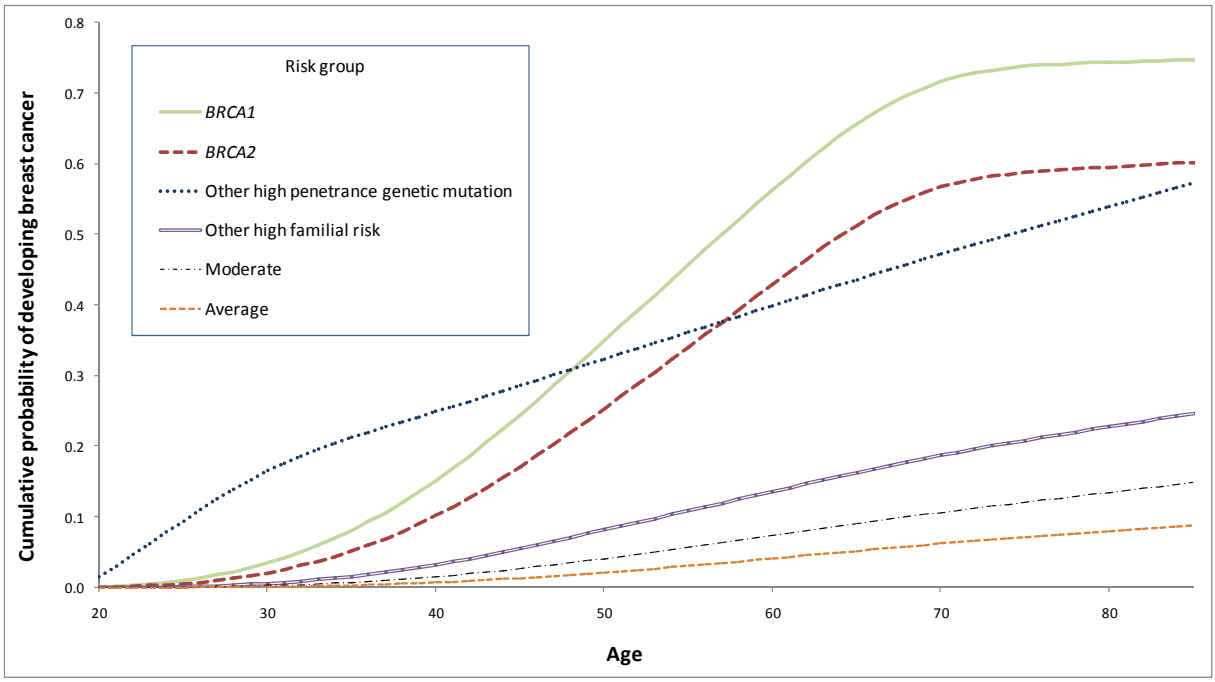
$$ERR = 0.74 * d_c * (age_c/50)^{-2}$$

Where ERR is the excess relative risk, d_c is the cumulative radiation dose, and age_c is the current age of the patient. The radiation therapy dose for two-view digital mammography was assumed to be 4.1mGy (95% CI: 1.8-6.7mGy).[130]

5.3.4 Probability of developing breast cancer

Data on the probability of developing breast cancer in a given year were derived from published evidence.[98;131-133] The probability of developing breast cancer by age is shown in Figure 5.2. Published data tend to provide cumulative probabilities by 10-year age bands. Smoothed probabilities by single year of age were estimated using a generalised additive model (GAM) approach.[134]

Figure 5.2 Cumulative probability of developing breast cancer by age and risk group



The 10-year probabilities of developing breast cancer for each risk group are given in Table 5.4.

Table 5.4 Ten-year probability of developing breast cancer by age and risk group

Age group	Risk level					
	BRCA1	BRCA2	Other high penetrance genetic mutation	High familial	Moderate	Average
20-29	0.029	0.017	0.153	0.005	0.002	0.001
30-39	0.107	0.073	0.089	0.024	0.011	0.005
40-49	0.192	0.147	0.075	0.048	0.024	0.014
50-59	0.214	0.175	0.075	0.054	0.032	0.019
60-69	0.165	0.148	0.074	0.052	0.034	0.021
70+	0.040	0.042	0.108	0.064	0.046	0.028

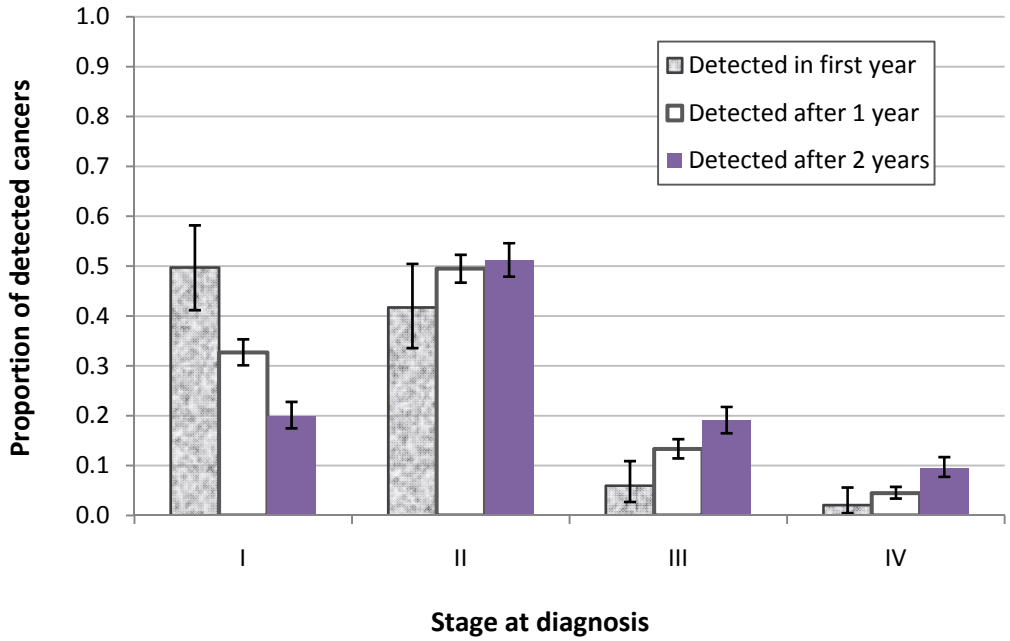
The probability of developing breast cancer is subject to uncertainty for a variety of reasons, including the small sample sizes, difficulty in follow-up and the fact that only a subset of a risk group population is usually known. In addition, the probability of developing breast cancer is not homogeneous within a risk group. To partly account for the uncertainty in the data, the probabilities were varied by ±10% in the model.

If unconstrained, an individual woman could be modelled to repeatedly develop primary breast cancer. While this is biologically possible, it was felt that in practice a woman would likely receive full bilateral mastectomy after multiple cancers and, for modelling purposes, her cancer risk would reduce to zero. In the model, a constraint was placed so that an individual woman could not have more than three primary invasive breast cancers.

5.3.5 Breast cancer stage at diagnosis

The typical distribution of stage at diagnosis was assumed to be different depending on when a cancer is detected relative to when it developed (Figure 5.3). Data from the National Cancer Registry Ireland (NCRI) specify the mode of presentation, distinguishing between those who present on foot of screening, and those who present symptomatically. For the model, it was assumed that the distribution of stage at diagnosis for women presenting on foot of screening would apply to those detected in the same year as they developed cancer. For those detected one or two years after developing cancer, the distribution of stage at diagnosis for women presenting symptomatically was used. The distribution was adjusted to favour earlier stage at diagnosis in those detected after one year, and later stage at diagnosis after two years.

Figure 5.3 Breast cancer stage at diagnosis by time of detection



Note: figures estimated from NCRI data.

5.3.6 Treatment

Women who receive a positive test result from surveillance were presumed to be recalled for further testing. The additional testing comprises an ultrasound scan and biopsy and is assumed to be 100% sensitive and specific. Core needle biopsy or vacuum assisted needle biopsy can be performed under ultrasound guidance, stereotactic guidance or with an MR-guided approach. It was assumed that with a DMX surveillance strategy, 1% (95% CI: 0% to 4%) of biopsies were MR-guided. According to the EAG, in a strategy involving MRI, 30% (95% CI: 21% to 39%) of biopsies would be MR-guided. Rates of MR-guided biopsy were varied using a beta distribution. It was also assumed that 10% to 15% of true positives will receive a pre-operative MRI for staging purposes irrespective of the imaging technique used for surveillance and irrespective of risk-group. It is probable that in reality a pre-operative MRI is less likely where the surveillance imaging is MRI and more likely where the surveillance imaging is digital mammography.

Treatment pathways are stage specific and derived from a combination of local hospital databases, NCRI data for women aged less than 50 with symptomatic breast cancer diagnosed between 2007 and 2010, national hospital inpatient data, and EAG input. Expert clinician input was used to validate the treatment pathways. The percentage of patients receiving each treatment by stage at diagnosis is given in Table 5.5.

Table 5.5 Proportion of patients receiving each treatment type by stage at diagnosis

Treatment	Stage				
	DCIS	I	II	III	IV
Chemotherapy	0.005	0.45	0.55	0.70	0.60
Radiotherapy	0.40	0.80	0.75	0.70	0.15
Mastectomy	0.50	0.25	0.30	0.65	0.05
Wide local excision	0.50	0.70	0.55	0.10	0.05
Sentinel node biopsy	0.60	0.90	0.60	0.10	0.05
Axillary clearance	0.01	0.05	0.30	0.65	0.05
Endocrine treatment	0.20	0.80	0.75	0.75	0.75

Note: an individual patient may receive a variety of treatment types.

Source: adapted by the Expert Advisory Group from National Cancer Registry Ireland data.

In practice, it is likely that some treatment combinations are correlated so that one treatment is likely to either co-occur with another or else to be used instead of

another. It was not possible to determine these correlations. As these data were only used for determining treatment costs and not treatment effect, the impact on model results should not be substantial.

The percentage of patients receiving each kind of treatment was fluctuated using a beta distribution. For example, the percentage of patients with DCIS undergoing mastectomy was 50% with a 95% CI of 36% to 64%.

It was assumed that patients not surviving to five years would require end-of-life care which would comprise supportive care (e.g. radiotherapy) and terminal care (e.g. hospice care).[135]

5.3.7 Mortality

Mortality was modelled based on both mortality from breast cancer and mortality from all other causes. Breast cancer mortality by stage at diagnosis was derived from the five-year survival data reported by the NCRI for the 2007-2009 cohort of breast cancer patients (Table 5.6). For all other causes of mortality, data were taken from the Irish life tables.[127] All-cause mortality was assumed to be comparable to mortality from all causes other than breast cancer. It was assumed that mortality due to DCIS was effectively zero.

Table 5.6 Five-year breast cancer mortality by age and stage at diagnosis

Age band	Stage I	Stage II	Stage III	Stage IV
20-29	0.008	0.162	0.474	0.830
30-39	0.080	0.086	0.337	0.574
40-49	0.012	0.074	0.291	0.828
50-59	0.019	0.101	0.263	0.622
60-69	0.040	0.112	0.368	0.733
70-79	0.040	0.112	0.368	0.733
80-89	0.040	0.112	0.368	0.733

Source: National Cancer Registry Ireland data.

It was assumed that women with stage IV cancer who do not survive to five years will survive for one to three years (median two years) based on a mean of 18-month survival from a possible 60 months.[135] For terminal stage IV cases, active treatment continues until the final year, when end-of-life care applies. It was assumed that women with stage I to III cancer who do not survive to five years initially go into remission before developing stage IV cancer in the final year of survival. These women receive stage IV treatment and end-of-life care in the final year of survival.

5.3.8 Health-related quality of life (HRQoL)

HRQoL was expressed as utility values and used to compute quality-adjusted life years (QALYs). Utilities can range from zero (death) to one (perfect health). It was assumed that average HRQoL decreases with increasing age, with the rate of decline taken from UK data.[120] According to these data, HRQoL declines from 0.9362 at age 20 to 0.7231 at age 85. HRQoL during treatment was assumed to be stage specific (Table 5.7).[136]

Table 5.7 Estimated HRQoL during treatment by stage at diagnosis[136]

Stage at diagnosis	HRQoL during treatment Mean	(95% CI)
DCIS	0.80	(0.72 to 0.87)
Stage I	0.72	(0.63 to 0.80)
Stage II	0.66	(0.56 to 0.75)
Stage III	0.61	(0.51 to 0.70)
Stage IV	0.45	(0.36 to 0.55)

Similarly, women who die from breast cancer were assumed to have a quality of life 0.35 (95% CI: 0.26-0.45) times that for normal health at the same age in the period from detection to death. A disutility was associated with false positives such that during the year of a false positive, a woman's HRQoL would be 0.998 times (95% CI: 0.975 to 0.999) times that for normal health at the same age.[137] No disutility was associated with false negatives under the assumption that if disease was sufficiently advanced to cause disutility, then it would be detected as a consequence of medical examination. All HRQoL parameters were defined using beta distributions with the alpha and beta parameters selected to reflect the reported mean HRQoL.

5.3.9 Costs

Costs were associated with surveillance, further testing of positive test results, and treatment of confirmed cases of breast cancer (Table 5.8). The cost of chemotherapy was specific to the stage of disease (node status) and receptor status (e.g., HER2, triple negative disease) and includes costs of supportive medications and monitoring relevant to the administration of chemotherapy. The cost of endocrine treatment was specific to whether the patient was pre- or post-menopausal. It was assumed that 0% of women were menopausal prior to age 40, 7% in the 40-44 year age band, 34% in the 45-49 year age band, 77% in the 50-54 year age band, and 100% thereafter.[138] A detailed description of how the unit costs applied in this HTA were derived is available in Appendix 3.

Table 5.8 Costs used in the economic model (2013 data)

Cost item	Source	Cost (€)
Digital mammogram	BreastCheck	102.50
MRI	Micro-costing	259.06
Ultrasound scan	RCC	88.67
Biopsy (core needle or vacuum)	RCC	502.32
Biopsy (MR-guided)	RCC	1,334.50
Chemotherapy	RCC	17,415.00
Radiotherapy	DRG	6,310.00
Mastectomy	DRG	7,963.00
Wide local excision	DRG	4,094.00
Sentinel node biopsy	DRG	3,291.00
Axillary clearance	DRG	4,849.00
Endocrine treatment	PCRS	1,820.00
End-of-life care	UK[135]	4,903.00

Abbreviations: RCC – regional cancer centre; DRG – diagnosis-related group; MRI – magnetic resonance imaging; PCRS – Primary Care Reimbursement Service.

Based on national hospital inpatient data, it was determined that sentinel node biopsy and axillary clearance occur as the primary procedure in approximately 18% of episodes that include a mastectomy or wide local excision. Hence, it is assumed that in 82% of cases the cost of sentinel node biopsy or axillary clearance is included in the cost of the primary procedure (i.e. mastectomy or wide local excision).

Costs were varied in each simulation according to a log normal distribution so that the 2.5th and 97.5th percentiles were approximately 20% below and 25% above the base-case value, respectively. For digital mammogram, MRI and ultrasound, the distribution was determined using observed data.[139]

5.3.10 Budget impact specific parameters

A number of parameters were defined specifically for the BIA to enable a real-world situation to be modelled.

Whereas the cost-utility analysis assumed 100% uptake of surveillance, for the BIA it was assumed that not all women would present at screening. It was assumed that uptake was age-specific and was equivalent for all elevated risk subgroups (Table 5.9).[140] It was assumed that the same uptake rates would apply irrespective of imaging modality or surveillance frequency.

Table 5.9 Estimated surveillance uptake by age

Age group	Uptake (%) Median	(95% CI)
20-29	56.3	(31.9 – 78.8)
30-39	77.0	(66.1 - 86.5)
40-49	95.7	(90.8 – 98.8)
50+	97.5	(93.1 – 99.7)

It was assumed that some proportion of women would avail of prophylactic mastectomy as a primary preventive measure, and that for these surveillance would no longer be necessary. It was assumed that prophylactic surgery would either take place when a woman was identified as being at elevated risk, or else as part of treatment for symptomatic breast cancer. The rate of prophylactic surgery was specific to risk level (Table 5.10).[141] Both the uptake and prophylactic surgery parameters were defined using beta distributions.

Table 5.10 Estimated uptake of prophylactic surgery by risk status

Risk status	Uptake (%) Median	(95% CI)
BRCA1/2 or other high penetrance genetic mutation	17.9	(15.9 – 20.0)
High familial risk	2.5	(1.8 – 3.2)
Moderate risk	1.7	(1.0 – 2.7)

For the BIA, it was assumed that women who become pregnant would not avail of surveillance for two consecutive six-month cycles. It was assumed that the rate of pregnancy for women at elevated risk of developing breast cancer was equivalent to that of the general population,[142] rising from 0.036 at age 20 to a maximum of 0.134 at age 34 and then decreasing to 0 by age 50.

5.4 Results of the cost-utility analysis

The model was run separately for a number of risk subgroups: *BRCA1* mutation carriers; *BRCA2* mutation carriers; other high penetrance genetic mutations; high familial risk with no identified genetic mutation; and moderate risk. A variety of surveillance strategies was modelled for each risk group. Each scenario was evaluated over 75,000 model simulations during which all of the main parameters were varied. The cost-utility analysis modelled a cohort of 1,000 women from age 20 to life expectancy. No surveillance and current ad hoc surveillance were also modelled. The discounted cost and QALYs associated with each strategy were estimated, along with a number of other outputs including number of cancers

screen- and symptom-detected and breast cancer mortality in the cohort at age 50. The estimated budget impact over five years for the known population in each subgroup is also presented.

Tables with cost-effectiveness results are rank sorted by decreasing average QALYs per person, so that the most effective strategy is at the top and the least effective strategy is at the bottom. For budget impact, strategies are rank-sorted by increasing total budget impact.

The cost-effectiveness plane is also presented for each risk group. In the cost-effectiveness plane, strategies are plotted according to their incremental benefit on the horizontal axis (in QALYs) and incremental cost (on the vertical axis) relative to a common comparator, in this case 'no surveillance'. If an intervention is less costly and more effective than a comparator, then it is considered to dominate the comparator and would be the preferred option. A strategy that is more costly and less effective than the comparator is said to be dominated and would not be considered a cost-effective strategy. The cost-effectiveness frontier identifies the strategies that, for a given level of cost, have the maximum effect.

Cost-effectiveness acceptability curves (CEACs) are also presented. These plots show the probability that a strategy is the most effective for a given willingness-to-pay threshold. The willingness-to-pay threshold represents the amount society may be willing to pay for a benefit, in this case QALYs. For a given threshold, the CEAC indicates which strategy has the highest probability of delivering the greatest net benefit.

5.4.1 *BRCA1* subgroup

As documented in Table 5.2, the known population of *BRCA1* women aged less than 50 years was estimated to be 160 (95% CI: 87 to 237). The average number of QALYs per person is 19.72 for no surveillance. Based on the results for individual five-year age bands, a number of strategies were defined for full evaluation (Table 5.11). It is assumed that current ad hoc surveillance is defined by a combination of strategies A14 and A15, which are differentiated by the age at which MRI is combined with DMX. The results for the full strategies tested are given in Table 5.11 below ordered by effectiveness. The most effective strategy was annual MRI surveillance from age 25 (A19) followed by annual MRI surveillance from age 25 to 39 combined with annual DMX from age 40 (A18). A number of strategies have similar efficacy, but differ in the cost per person. In terms of mortality reduction, a number of strategies are estimated to achieve similar reductions.

Table 5.11 Surveillance strategies for women with *BRCA1* mutations sorted by effectiveness

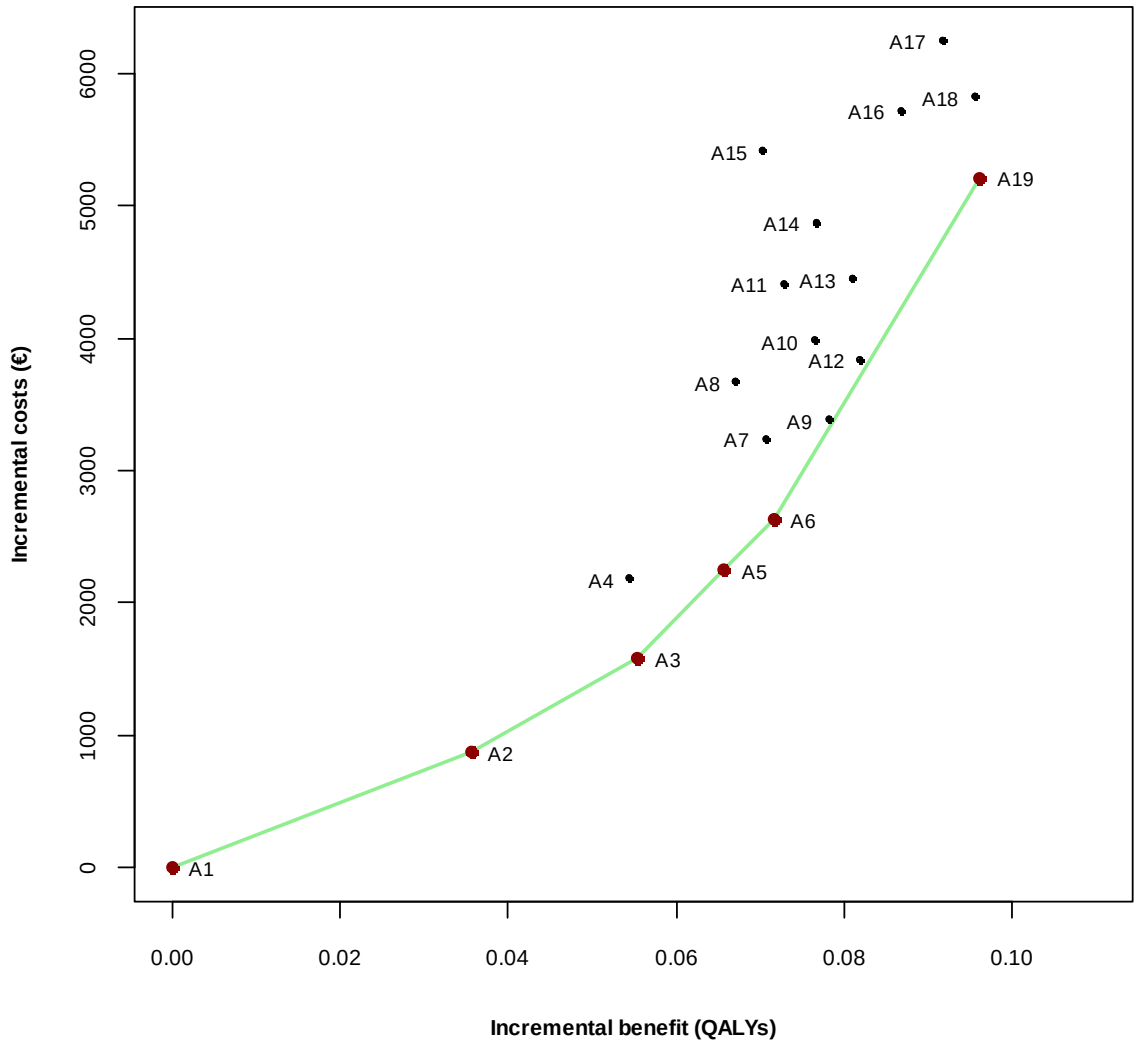
Strategy	Surveillance by age					Per person				Per 1,000 women*		
	20-24	25-29	30-34	35-39	40-49	QALYs	Cost	Screens	ICER	Screen detected	Symptom detected	BC mortality at 50
A19	None	MRI (12)	MRI (12)	MRI (12)	MRI (12)	19.8150	10,763	24.4	54,193	384	395	32
A18	None	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	19.8144	11,366	24.4	60,816	395	400	32
A17	None	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.8105	11,800	24.4	68,124	403	402	32
A16	None	MRI (24)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.8057	11,266	22.4	65,812	401	404	33
A12	None	None	MRI (12)	MRI (12)	MRI (12)	19.8008	9,388	19.4	46,820	363	415	34
A13	None	None	MRI (12)	MRI (12)	DMX+MRI (12)	19.7998	9,992	19.4	54,838	374	420	33
A09	None	None	MRI (24)	MRI (12)	MRI (12)	19.7970	8,927	17.4	43,174	359	419	34
A14	None	None	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.7955	10,423	19.4	63,530	382	422	33
A10	None	None	MRI (24)	MRI (12)	DMX+MRI (12)	19.7954	9,531	17.4	52,009	369	424	34
A11	None	None	MRI (24)	DMX+MRI (12)	DMX+MRI (12)	19.7918	9,960	17.4	60,462	377	426	34
A06	None	None	None	MRI (12)	MRI (12)	19.7904	8,182	14.5	36,770	318	459	35
A07	None	None	None	MRI (12)	DMX+MRI (12)	19.7895	8,785	14.5	45,758	328	464	34
A15	None	None	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.7893	10,959	19.4	76,776	392	424	34
A08	None	None	None	DMX+MRI (12)	DMX+MRI (12)	19.7860	9,218	14.5	54,590	337	466	35
A05	None	None	None	MRI (24)	MRI (12)	19.7845	7,794	12.5	34,146	310	466	36
A03	None	None	None	None	MRI (12)	19.7742	7,133	9.5	28,582	243	530	37
A04	None	None	None	None	DMX+MRI (12)	19.7734	7,732	9.5	39,977	255	534	37
A02	None	None	None	None	MRI (24)	19.7544	6,419	4.8	24,441	199	571	40
A01	None	None	None	None	None	19.7188	5,548	0.0	-	0	753	46

Abbreviations: ICER – incremental cost-effectiveness ratio [relative to no surveillance]; BC – breast cancer; DMX - digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging; QALYs – quality-adjusted life years.

** Estimated known population of female BRCA1 mutation carriers less than 50 years of age is 160 in Ireland.*

The cost-effectiveness plane of surveillance strategies for *BRCA1* mutation carriers is given in Figure 5.4 below. The cost-effectiveness frontier is defined by MRI-based strategies. Current ad hoc surveillance practice is defined as either A14 or A15 (annual MRI from age 30 combined with annual DMX from ages 35 and 30, respectively), both of which are above the frontier. In other words, these strategies are more costly than alternative strategies for a given level of effect. Strategies A9 and A12 are close to the frontier and may be considered efficient strategies.

Figure 5.4 Cost-effectiveness plane for surveillance strategies for women with *BRCA1* mutations



The cost-effectiveness frontier includes only MRI-based strategies (Table 5.12). Relative to 'no surveillance', MRI every 24 months from age 40 (A02) has an incremental cost-effectiveness ratio (ICER) of €24,441/QALY.

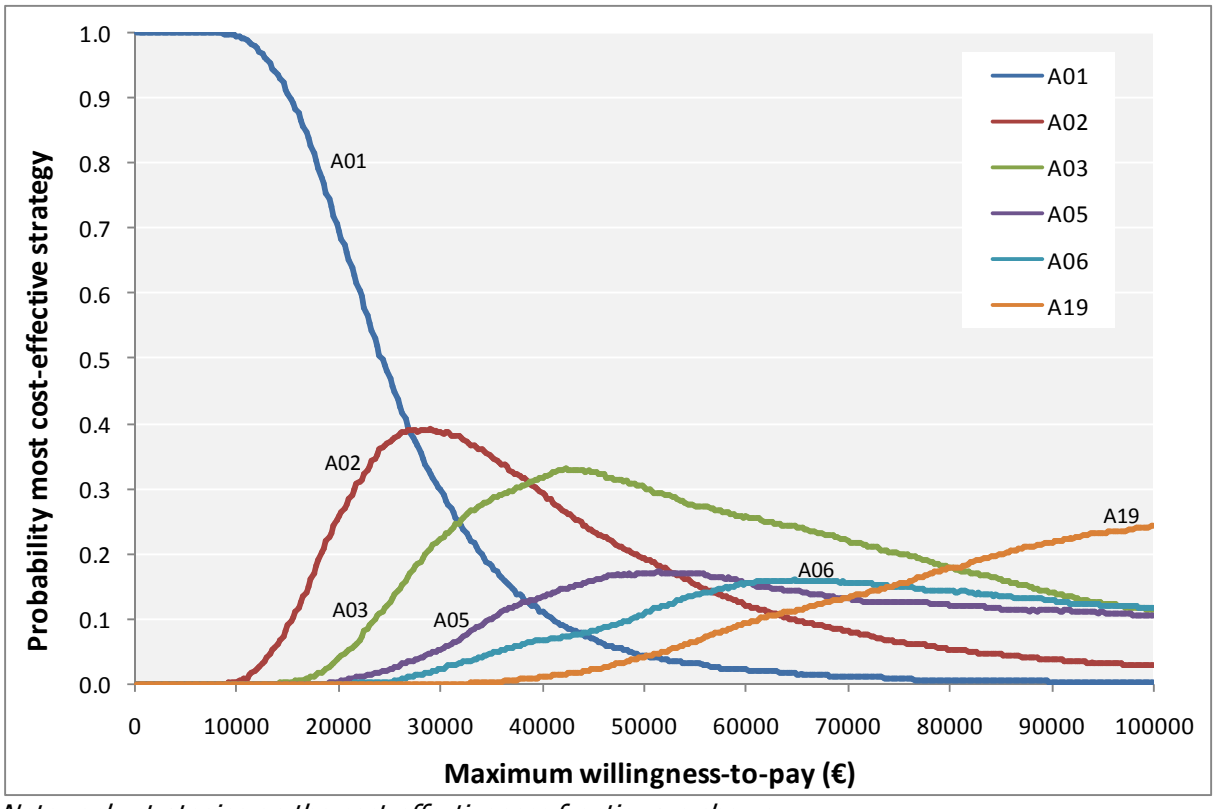
Table 5.12 ICERs for surveillance strategies on the frontier for the *BRCA1* subgroup

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER	Probability cost-effective	
						€20k/ QALY	€45k/ QALY
A01	19.7188	5,548	-	-	-	-	-
A02	19.7544	6,419	0.0356	871	24,441	0.29	0.85
A03	19.7742	7,133	0.0554	1,584	28,582	0.12	0.86
A05	19.7845	7,794	0.0658	2,245	34,146	0.03	0.76
A06	19.7904	8,182	0.0716	2,633	36,770	0.01	0.70
A19	19.8150	10,763	0.0962	5,215	54,193	0.00	0.28

Note: ICER – incremental cost-effectiveness ratio relative to no surveillance (strategy A01). ICERs relative to next best strategy reported in Appendix 4.

The cost-effectiveness acceptability curves are presented in Figure 5.5. At a willingness-to-pay threshold of €20,000 per QALY and up to a willingness-to-pay threshold of €27,000 per QALY, no surveillance is likely to be the most cost-effective option. At increasing thresholds, strategies A2, A3 and A19 have the highest probabilities of being cost-effective.

Figure 5.5 Cost-effectiveness acceptability curves for surveillance strategies for *BRCA1* mutation carriers



Note: only strategies on the cost-effectiveness frontier are shown.

The budget impact and main resource use over five years for each strategy is presented in Table 5.13. 'No surveillance' is the least expensive option in terms of budget impact, generating no additional imaging over and above imaging for women who present symptomatically. The surveillance strategies all fall within a €93,746 range from strategy A02 (biennial MRI from age 40-49), the least expensive at €263,577 to €357,323 for strategy A17 (annual MRI from age 25-49 combined with annual DMX from age 35-49). Relative to existing ad hoc surveillance, all strategies evaluated had a similar or lower budget impact. With earlier start ages there are more false positives and consequently a greater need for further testing. However, due to the small size of the known population in this subgroup, the number of false positives is small.

Table 5.13 Budget impact and resource use of surveillance strategies for the known *BRCA1* subgroup sorted by budget impact

Strategy	Surveillance by age					Resource use over five years					
	20-24	25-29	30-34	35-39	40-49	Budget impact (€)	False positives	DMX	MRI	Further testing	MR-guided biopsies
A01	None	None	None	None	None	219,806	0	0	3	12	0
A02	None	None	None	None	MRI (24)	263,577	5	0	65	18	2
A03	None	None	None	None	MRI (12)	300,522	10	0	132	24	4
A05	None	None	None	MRI (24)	MRI (12)	311,910	12	0	150	26	5
A06	None	None	None	MRI (12)	MRI (12)	318,990	13	0	162	27	5
A04	None	None	None	None	DMX+MRI (12)	322,034	15	124	133	29	6
A09	None	None	MRI (24)	MRI (12)	MRI (12)	323,736	14	0	173	28	6
A12	None	None	MRI (12)	MRI (12)	MRI (12)	327,219	15	0	179	29	6
A19	None	MRI (12)	MRI (12)	MRI (12)	MRI (12)	330,274	15	0	186	30	6
A07	None	None	None	MRI (12)	DMX+MRI (12)	340,290	18	124	164	32	7
A10	None	None	MRI (24)	MRI (12)	DMX+MRI (12)	345,333	19	124	174	33	7
A08	None	None	None	DMX+MRI (12)	DMX+MRI (12)	345,352	19	154	165	34	7
A13	None	None	MRI (12)	MRI (12)	DMX+MRI (12)	348,537	19	124	181	34	7
A11	None	None	MRI (24)	DMX+MRI (12)	DMX+MRI (12)	350,690	20	154	175	35	8
A18	None	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	351,580	20	124	188	35	8
A14	None	None	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	353,952	21	154	181	35	8
A16	None	MRI (24)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	356,128	21	154	186	36	8
A15	None	None	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	356,631	21	171	182	36	8
A17	None	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	357,323	21	154	189	36	8

Abbreviations: DMX – digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging.

5.4.1.1 Interpretation of results for the BRCA1 subgroup

The incremental cost-effectiveness ratios relative to no surveillance for all of the strategies on the cost-effectiveness frontier are below or close to a notional cost-effectiveness threshold of €45,000/QALY, indicating that any of these strategies likely constitutes a cost-effective use of healthcare resources in Ireland compared to no surveillance. With the exception of A19 (annual MRI from age 25), each strategy costs less than the current ad hoc surveillance – a combination of strategies A14 and A15, annual MRI from age 30 combined with annual DMX from age 35 (A14) or age 30 (A15) – but also delivers less in terms of benefits measured in QALYS and impact on mortality. Strategy A19 has a similar cost to A14 and A15 and has a small gain in terms of QALYs and mortality. Commencing MRI surveillance at 30 with or without the addition of mammography from age 40 (strategies A12 and A13) offers a small health gain over current ad hoc surveillance at a slightly reduced cost. Strategies A09, A10 and A11 also offer similar benefits to ad hoc surveillance at lower cost, but all three involve biennial surveillance from age 30 to 34. The evidence underpinning the higher sensitivity of biennial screening is limited and may overestimate the benefits of that surveillance frequency.

If the primary concern of the decision maker is to maximise health gain for this cohort of women for a given budget while at a minimum maintaining current effectiveness, A12 (annual MRI from age 30) and A19 (annual MRI from age 25) are the optimal strategies, but incurring an incremental five-year budget impact of approximately €110,000 relative to no surveillance. However, given current international practice, it is recognised that there may be some reluctance amongst clinicians to adopt a surveillance strategy based on MRI alone. In this case, strategy A13 (annual MRI from age 30 combined with annual DMX starting at age 40) at a slightly increased incremental budget impact of €129,000 relative to no surveillance over five years, slightly fewer QALYs and the same mortality reduction may be a reasonable choice in terms of cost-effectiveness and benefit delivered. The budget impact is based on the estimated known population in Ireland of 160 women. The budget impact is directly proportional to the number of identified women and hence increases if the known population increases.

5.4.2 *BRCA2* subgroup

As outlined in Table 5.2, the known female population of *BRCA2* mutation carriers less than 50 years of age was estimated to be 117 (95% CI: 52 to 198). The average number of QALYs per person is 19.86 for no surveillance. Based on the results for individual five-year age bands (Appendix 4), a number of strategies were defined for full evaluation; these were identical to those defined for the *BRCA1* subgroup (Table 5.14). As for the *BRCA1* subgroup, the most effective strategy was annual MRI

surveillance from age 25 (B19) followed by annual MRI surveillance from age 25 to 39 combined with annual DMX from age 40 (B18). The cost variation across strategies is marginally less than observed for the *BRCA1* cohort. In terms of mortality reduction, a number of strategies are estimated to achieve similar reductions, but the scope for mortality reduction is much less than for the *BRCA1* cohort.

Table 5.14 Surveillance strategies for *BRCA2* mutation carriers sorted by effectiveness

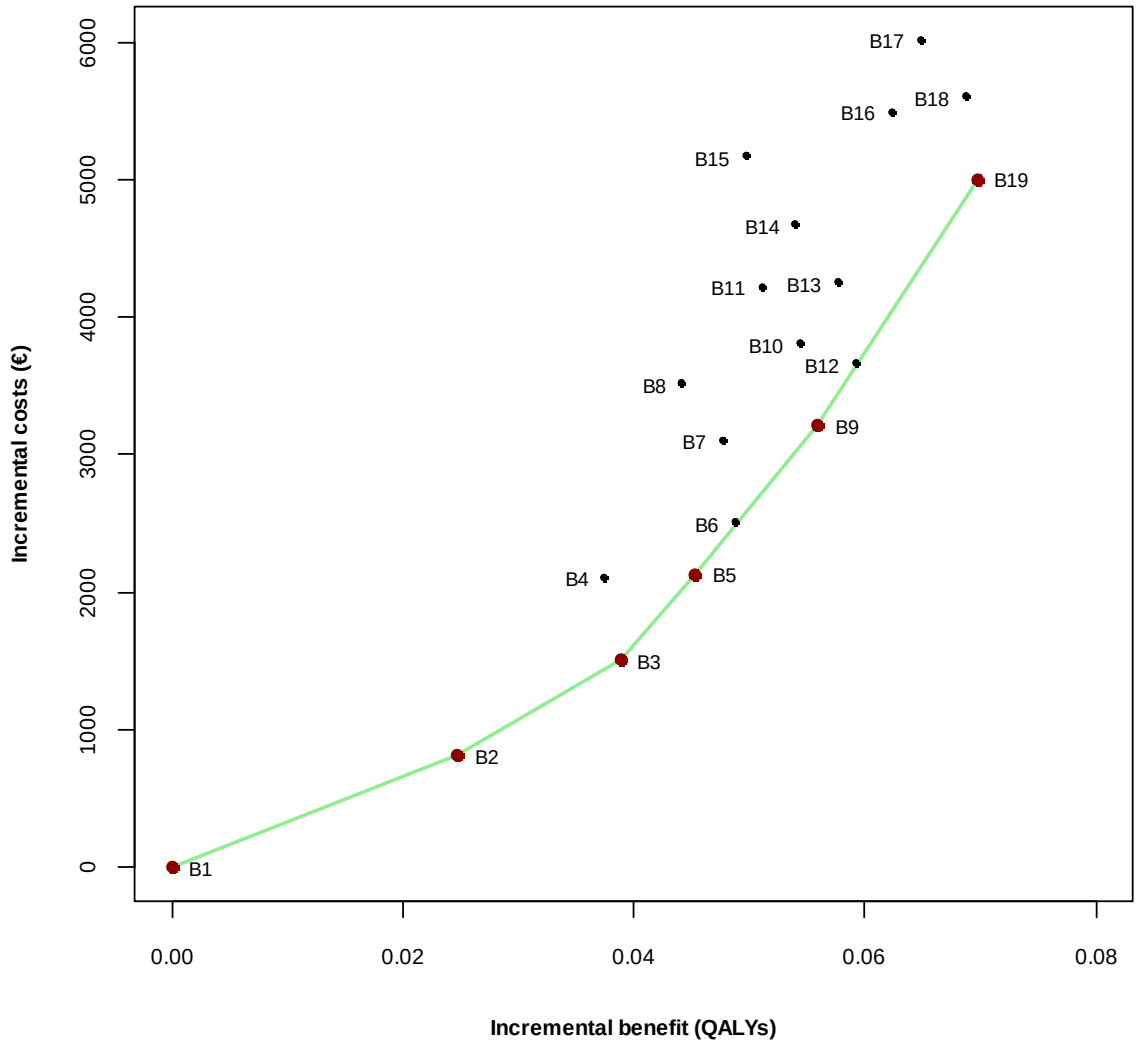
Strategy	Surveillance by age					Per person				Per 1,000 women		
	20-24	25-29	30-34	35-39	40-49	QALYs	Cost	Screens	ICER	Screen-detected	Symptom-detected	BC mortality at 50
B19	None	MRI (12)	MRI (12)	MRI (12)	MRI (12)	19.9330	9,203	24.6	71,780	275	327	23
B18	None	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	19.9321	9,803	24.6	81,466	284	331	23
B17	None	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.9282	10,214	24.6	92,681	289	334	23
B16	None	MRI (24)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.9256	9,686	22.6	87,972	288	335	23
B12	None	None	MRI (12)	MRI (12)	MRI (12)	19.9226	7,856	19.6	61,665	264	337	24
B13	None	None	MRI (12)	MRI (12)	DMX+MRI (12)	19.9210	8,451	19.6	73,684	273	341	24
B09	None	None	MRI (24)	MRI (12)	MRI (12)	19.9192	7,410	17.6	57,441	262	339	25
B10	None	None	MRI (24)	MRI (12)	DMX+MRI (12)	19.9177	8,006	17.6	69,937	270	344	24
B14	None	None	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.9173	8,866	19.6	86,391	278	343	24
B11	None	None	MRI (24)	DMX+MRI (12)	DMX+MRI (12)	19.9144	8,415	17.6	82,444	275	346	24
B15	None	None	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.9131	9,370	19.6	103,876	285	346	24
B06	None	None	None	MRI (12)	MRI (12)	19.9121	6,703	14.6	51,310	235	365	25
B07	None	None	None	MRI (12)	DMX+MRI (12)	19.9110	7,299	14.6	64,977	243	370	25
B05	None	None	None	MRI (24)	MRI (12)	19.9086	6,330	12.6	47,024	230	370	26
B08	None	None	None	DMX+MRI (12)	DMX+MRI (12)	19.9075	7,710	14.6	79,454	248	372	25
B03	None	None	None	None	MRI (12)	19.9021	5,707	9.6	38,877	184	414	27
B04	None	None	None	None	DMX+MRI (12)	19.9008	6,302	9.6	56,086	193	418	27
B02	None	None	None	None	MRI (24)	19.8880	5,016	4.8	33,079	150	447	29
B01	None	None	None	None	None	19.8633	4,199	0.0	-	0	586	33

Abbreviations: ICER – incremental cost-effectiveness ratio [relative to no surveillance]; BC – breast cancer; DMX - digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging; QALYs – quality-adjusted life years.

** Estimated known population of female BRCA2 mutation carriers less than 50 years of age is 117 in Ireland.*

The cost-effectiveness plane of surveillance strategies for *BRCA2* mutation carriers is given in Figure 5.6 below. As for the *BRCA1* subgroup, current surveillance is assumed to be a combination of strategies B14 and B15. These two strategies are not on the cost-effectiveness frontier, indicating that these strategies are more costly than alternative strategies for a given level of effect. Two of the strategies, B6 and B12 are arbitrarily close to the frontier and may be considered efficient strategies.

Figure 5.6 Cost-effectiveness plane for surveillance strategies for *BRCA2* mutation carriers



As for the *BRCA1* subgroup, the cost-effectiveness frontier includes only MRI-based strategies (Table 5.15). Relative to a strategy of 'no surveillance', MRI every 24 months from age 40 (B02) has an incremental cost-effectiveness ratio of €33,079. Strategy B03 (annual MRI from age 40) also is below a notional threshold of €45,000 per QALY.

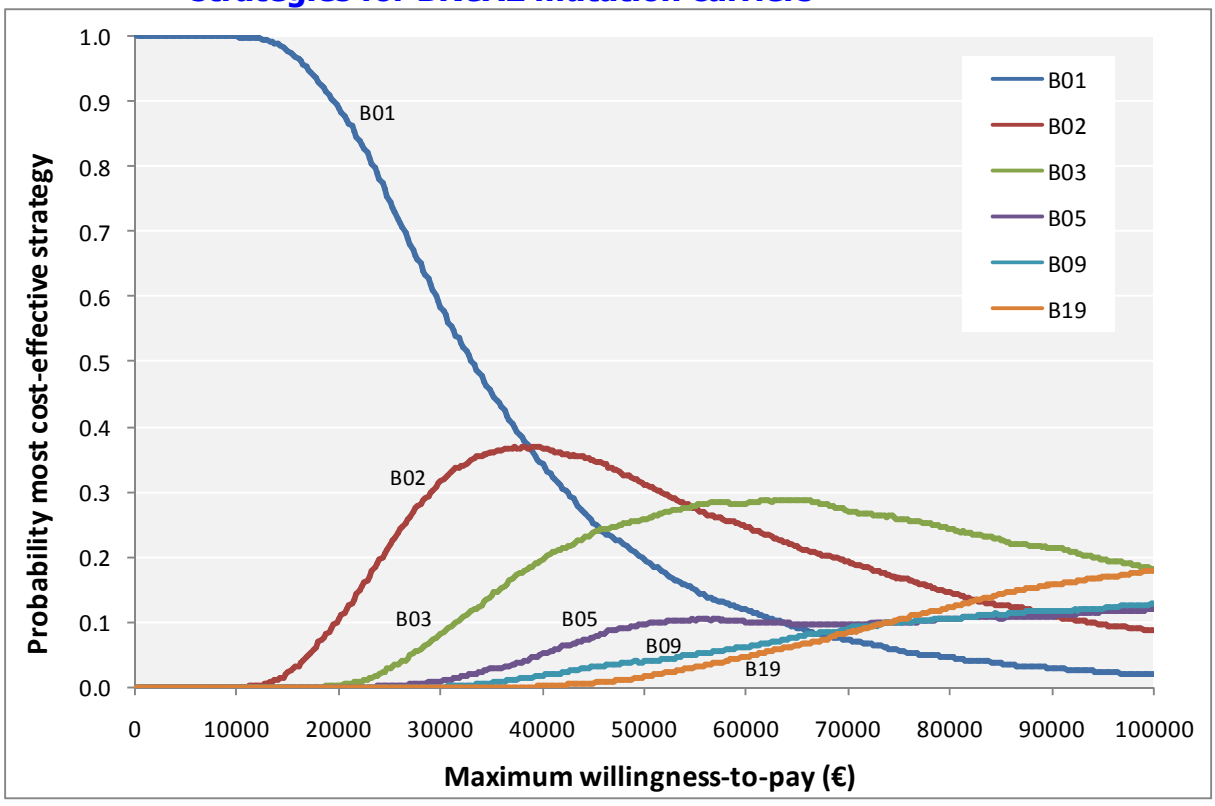
Table 5.15 ICERs for surveillance strategies on the frontier for the *BRCA2* subgroup

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER	Probability cost-effective	
						€20k/ QALY	€45k/ QALY
B01	19.8633	4,199	-	-	-	-	-
B02	19.8880	5,016	0.0247	817	33,079	0.13	0.67
B03	19.9021	5,707	0.0388	1,509	38,877	0.02	0.59
B05	19.9086	6,330	0.0453	2,132	47,024	0.01	0.41
B09	19.9192	7,410	0.0559	3,212	57,441	0.00	0.22
B19	19.9330	9,203	0.0697	5,005	71,780	0.00	0.06

Note: ICER – incremental cost-effectiveness ratio relative to no surveillance (strategy B01). ICERs relative to next best strategy reported in Appendix 4.

The cost-effectiveness acceptability curves are presented in Figure 5.7. Only strategies on the cost-effectiveness frontier have been included. At a willingness-to-pay threshold of €20,000 per QALY and up to a willingness to pay threshold of €38,000, no surveillance is likely to be the most cost-effective option. At a willingness-to-pay threshold of €45,000 per QALY, there is a probability of 0.35 that strategy B02 is the most cost-effective option.

Figure 5.7 Cost-effectiveness acceptability curves for surveillance strategies for *BRCA2* mutation carriers



Note: only strategies on the cost-effectiveness frontier are shown.

The five-year budget impact of 'no surveillance' is the least expensive option in terms of budget impact, costing €126,603 over five years for the 117 identified women (Table 5.16). The surveillance strategies all fall within a €63,912 range from €154,953 for strategy B02 (biennial MRI starting at age 40 years) to €218,865 for strategy B15 (annual DMX plus MRI starting at age 30 years). The additional cost of surveillance therefore ranges from €28,350 to €92,262 for strategies B02 and B15, respectively. As with the *BRCA1* subgroup, the strategies that most likely represent current ad hoc surveillance are amongst the strategies with the highest five-year budget impact.

Table 5.16 Budget impact and resource use of surveillance strategies for the known *BRCA2* subgroup sorted by budget impact

Strategy	Surveillance by age					Resource use over five years					
	20-24	25-29	30-34	35-39	40-49	Budget impact (€)	False positives	DMX	MRI	Further testing	MR-guided biopsies
B01	None	None	None	None	None	126,603	0	0	2	7	0
B02	None	None	None	None	MRI (24)	154,953	4	0	46	11	1
B03	None	None	None	None	MRI (12)	181,316	8	0	95	16	3
B05	None	None	None	MRI (24)	MRI (12)	187,874	9	0	108	17	3
B06	None	None	None	MRI (12)	MRI (12)	192,601	10	0	117	18	4
B09	None	None	MRI (24)	MRI (12)	MRI (12)	196,146	10	0	125	18	4
B04	None	None	None	None	DMX+MRI (12)	196,984	11	90	96	19	4
B12	None	None	MRI (12)	MRI (12)	MRI (12)	198,130	11	0	129	19	4
B19	None	MRI (12)	MRI (12)	MRI (12)	MRI (12)	200,595	11	0	135	19	4
B07	None	None	None	MRI (12)	DMX+MRI (12)	207,702	13	90	118	21	5
B08	None	None	None	DMX+MRI (12)	DMX+MRI (12)	211,033	14	112	118	22	5
B10	None	None	MRI (24)	MRI (12)	DMX+MRI (12)	211,539	14	90	126	22	5
B13	None	None	MRI (12)	MRI (12)	DMX+MRI (12)	213,660	14	90	130	23	5
B11	None	None	MRI (24)	DMX+MRI (12)	DMX+MRI (12)	214,719	15	112	126	23	5
B18	None	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	215,479	15	90	136	23	5
B14	None	None	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	216,991	15	112	130	23	5
B16	None	MRI (24)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	218,113	15	112	134	24	5
B17	None	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	218,834	16	112	136	24	5
B15	None	None	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	218,865	16	123	131	24	5

Abbreviations: DMX – digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging.

5.4.2.1 Interpretation of results for the BRCA2 subgroup

Similar to the *BRCA1* analysis, the incremental cost-effectiveness ratios relative to no surveillance for most of the strategies on the cost-effectiveness frontier are close to a notional cost-effectiveness threshold of €45,000/QALY. As such, most of these strategies likely constitute a cost-effective alternative compared to no surveillance. With the exception of B19 (annual MRI from age 25) and B9, each strategy costs less than the current ad hoc surveillance – a combination of strategies B14 and B15; annual MRI from age 30 combined with annual DMX from age 35 (B14) or age 30 (B15). Commencing MRI surveillance at 30 with or without the addition of mammography from age 40 (strategies A12 and A13) offers a small health gain over current ad hoc surveillance at a slightly reduced cost.

In attempting to maximise health gain for this cohort of women for a given budget while at a minimum maintaining current effectiveness, strategies B12 and B19 are the optimal strategies with an incremental five-year budget impact relative to no surveillance of €71,527 and €73,992, respectively. Should clinicians prefer to adopt a surveillance strategy based on both MRI and digital mammography, strategy B13 (annual MRI from age 30 combined with annual DMX from age 40) at a slightly increased incremental budget impact of €87,057 over five years, slightly fewer QALYs and the same mortality reduction, is a reasonable choice in terms of cost-effectiveness and benefit delivered.

5.4.3 Other high penetrance genetic mutations subgroup

As noted in Table 5.2, the known population of women aged less than 50 years with other high penetrance genetic mutations was estimated to be 80 (95% CI: 63 to 99). This risk group is distinctive for the high probability of breast cancer before the age of 30 in *TP53* mutation carriers. For this reason, a number of strategies were modelled starting at age 20 as is recommended in the 2006 NICE guidelines.[7]

The average number of QALYs per person is 19.48 for 'no surveillance' (Table 5.17). The most effective strategy was biannual MRI surveillance from age 20 (C02), followed by biannual MRI surveillance from age 20 to 29 combined with annual MRI from ages 30 to 49 (C07). The results for this cohort show the very substantial reductions in mortality that can be achieved relative to a strategy of no surveillance (Table 5.17). All strategies modelled have ICERs below, or close to a notional threshold of €45,000 per QALY relative to no surveillance.

Table 5.17 Surveillance strategies for women with other high penetrance genetic predispositions, sorted by effectiveness

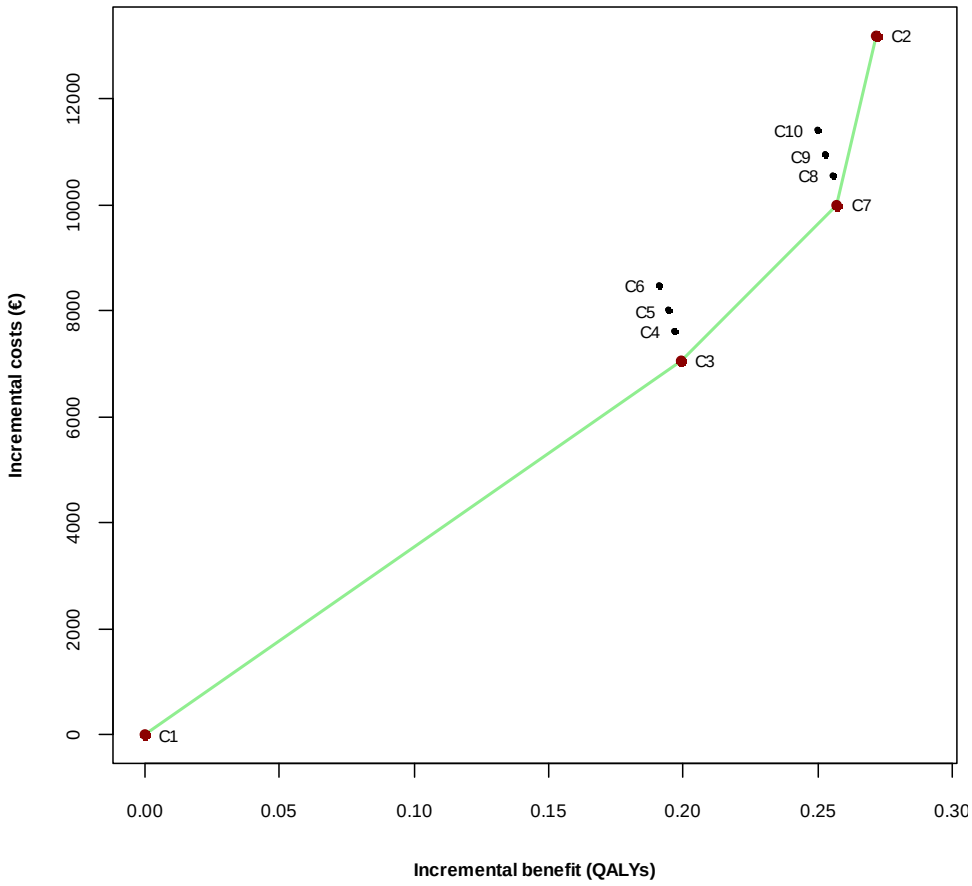
Strategy	Surveillance by age					Per person				Per 1,000 women*		
	20-24	25-29	30-34	35-39	40-49	QALYs	Cost	Screens	ICER	Screen-detected	Symptom-detected	BC mortality at 50
C02	MRI 6	MRI 6	MRI 6	MRI 6	MRI 6	19.7485	19,119	57.8	48,593	411	104	37
C07	MRI 6	MRI 6	MRI (12)	MRI (12)	MRI (12)	19.7337	15,915	38.8	38,929	397	118	39
C08	MRI 6	MRI 6	MRI (12)	MRI (12)	DMX+MRI (12)	19.7322	16,464	38.8	41,302	402	119	39
C09	MRI 6	MRI 6	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.7294	16,850	38.8	43,276	406	120	39
C10	MRI 6	MRI 6	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.7265	17,332	38.8	45,719	411	120	39
C03	MRI (12)	MRI (12)	MRI (12)	MRI (12)	MRI (12)	19.6757	12,986	29.0	35,542	387	124	43
C04	MRI (12)	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	19.6736	13,531	29.0	38,687	392	125	43
C05	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.6714	13,915	29.0	41,097	396	126	43
C06	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	19.6679	14,394	29.0	44,374	401	126	43
C01	None	None	None	None	None	19.4767	5,912	0.0	-	0	496	61

Abbreviations: DMX - digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging; QALYs – quality-adjusted life years; ICER – incremental cost-effectiveness ratio [relative to no surveillance]; BC – breast cancer.

** Estimated known population of women less than 50 years of age with other identified high penetrance genetic mutations is 80 in Ireland.*

The cost-effectiveness plane of surveillance strategies for women with high penetrance genetic mutations is given in Figure 5.8 below.

Figure 5.8 Cost-effectiveness plane for surveillance strategies for women with other high penetrance mutations



The cost-effectiveness frontier contains only purely MRI-based strategies (Table 5.18).

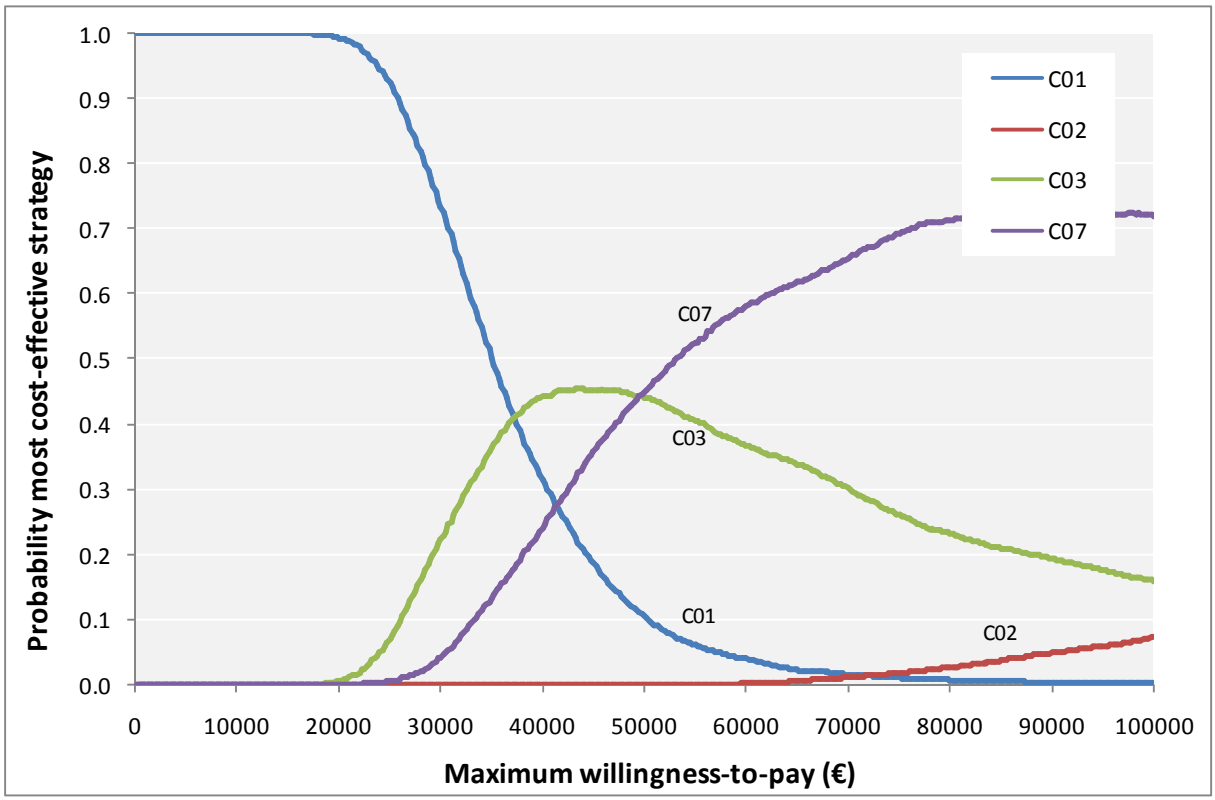
Table 5.18 ICERs for surveillance strategies for other high penetrance mutation carriers

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER	Probability cost-effective	
						€20k/ QALY	€45k/ QALY
C01	19.4767	5,912	-	-	-	-	-
C03	19.6757	12,986	0.1990	7,074	35,542	0.01	0.76
C07	19.7337	15,915	0.2570	10,003	38,929	0.00	0.71
C02	19.7485	19,119	0.2718	13,207	48,593	0.00	0.36

Note: ICER – incremental cost-effectiveness ratio relative to no surveillance (strategy C01). ICERs relative to next best strategy reported in Appendix 4.

The cost-effectiveness acceptability curves are presented in Figure 5.9. Again, only strategies on the cost-effectiveness frontier are shown in the plot. Up to a willingness-to-pay threshold of €37,000 per QALY, no surveillance is likely to be the most cost-effective option. Above a threshold of €37,000 per QALY up to €49,500 per QALYS, a strategy of annual MRI from age 20 has the highest probability of offering the greatest expected net benefit.

Figure 5.9 Cost-effectiveness acceptability curves for surveillance strategies for other high penetrance mutation carriers



Note: only strategies on the cost-effectiveness frontier are shown.

As before, the five-year budget impact of 'no surveillance' is the least expensive option in terms of budget impact (Table 5.19). The surveillance strategies all fall within a €41,994 range from €92,497 for strategy C03 to €134,491 for strategy C02, which is also the most effective strategy. The incremental budget impact over five years compared to 'no surveillance' ranges from €43,527 to €85,521 for strategies C03 and C02, respectively. The relatively small budget impact is due to the small size of the known population in this risk subgroup.

Table 5.19 Budget impact and resource use of surveillance strategies for the known population of other high penetrance mutation carriers sorted by budget impact

Strategy	Surveillance by age					Resource use over five years					
	20-24	25-29	30-34	35-39	40-49	Budget impact (€)	False positives	DMX	MRI	Further testing	MR-guided biopsies
C01	None	None	None	None	None	48,970	0	0	1	3	0
C03	MRI (12)	MRI (12)	MRI (12)	MRI (12)	MRI (12)	92,497	8	0	93	11	3
C07	MRI 6	MRI 6	MRI (12)	MRI (12)	MRI (12)	94,981	8	0	98	12	3
C04	MRI (12)	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	102,337	10	62	94	14	3
C05	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	104,622	11	78	94	14	4
C08	MRI 6	MRI 6	MRI (12)	MRI (12)	DMX+MRI (12)	104,622	11	62	98	14	3
C06	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	105,938	11	86	94	15	4
C09	MRI 6	MRI 6	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	106,839	11	78	99	15	4
C10	MRI 6	MRI 6	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)	108,375	12	86	99	15	4
C02	MRI 6	MRI 6	MRI 6	MRI 6	MRI 6	134,491	16	0	189	20	5

Abbreviations: DMX – digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging.

5.4.3.1 Interpretation of results for the subgroup with other high penetrance mutation carriers

The incremental cost-effectiveness ratios relative to no surveillance of the three strategies on the cost-effectiveness frontier are below or close to a notional cost-effectiveness threshold of €45,000/QALY when compared to no surveillance. Under the assumption that current ad hoc surveillance is described by a combination of strategies C05 and C06 (annual MRI from age 20 combined with annual DMX from age 35 or age 30, for C05 and C06 respectively), all of the strategies on the frontier offer more health gain (greater QALY gain), but only strategy C03 (annual MRI from age 20) does so at a lower cost. All of the strategies on the frontier offer equivalent or lower mortality than current ad hoc surveillance.

To maximise health gain for this cohort of women for a given budget while at a minimum maintaining current effectiveness, C03 (annual MRI from age 20) is the optimal strategy (i.e. an incremental budget impact of €43,527 over five years compared to no surveillance). This is a surveillance strategy based on MRI alone, as are all the strategies on the cost-effectiveness frontier. The strategies that define current ad hoc surveillance are both close to the frontier and have ICERs close to a notional threshold of €45,000 when compared to a strategy of no surveillance, indicating that they may form acceptable strategies. Strategies C07 and C02 are cost-effective alternatives that deliver increased benefit over C03 for a small increase in incremental budget impact compared to no surveillance (€46,011 and €85,521 over five years, respectively). However, strategies comprising six-monthly MRI may not be considered ideal for a number of reasons (e.g. increased risk of false positives, MRI capacity constraints).

The risk subgroup comprises women with a range of identified high penetrance genetic mutations, one of which, *TP53*, has a disproportionately high risk before the age of 30. While annual or biennial MRI from age 20 may be cost-effective for the group as a whole, for those without a *TP53* mutation it may not provide a significant health gain to start surveillance before the age of 30. For women in this subgroup other than *TP53* mutation carriers, the risk of developing cancer is similar to that of *BRCA* mutation carriers and hence surveillance recommendations for the *BRCA* subgroup may be more appropriate.

5.4.4 High familial risk subgroup

The known population of women less than 50 years of age at high familial risk with no identified genetic mutations was estimated to be 1,674 (95% CI: 1,241 to 2,326) as noted in Table 5.2. The average number of QALYs per person is 20.16 for a 'no surveillance' option (Table 5.20). Strategies of annual and biennial DMX from age 30 were included as these contribute to the estimate of current ad hoc surveillance. The

most efficacious strategy was annual MRI surveillance from age 40 (D02) followed by combined MRI and DMX surveillance from age 40 (D03). The results for this cohort show very minor reductions in mortality that can be achieved relative to a strategy of no surveillance.

Table 5.20 Surveillance strategies for women at high familial risk, but with no identified genetic mutations, sorted by effectiveness

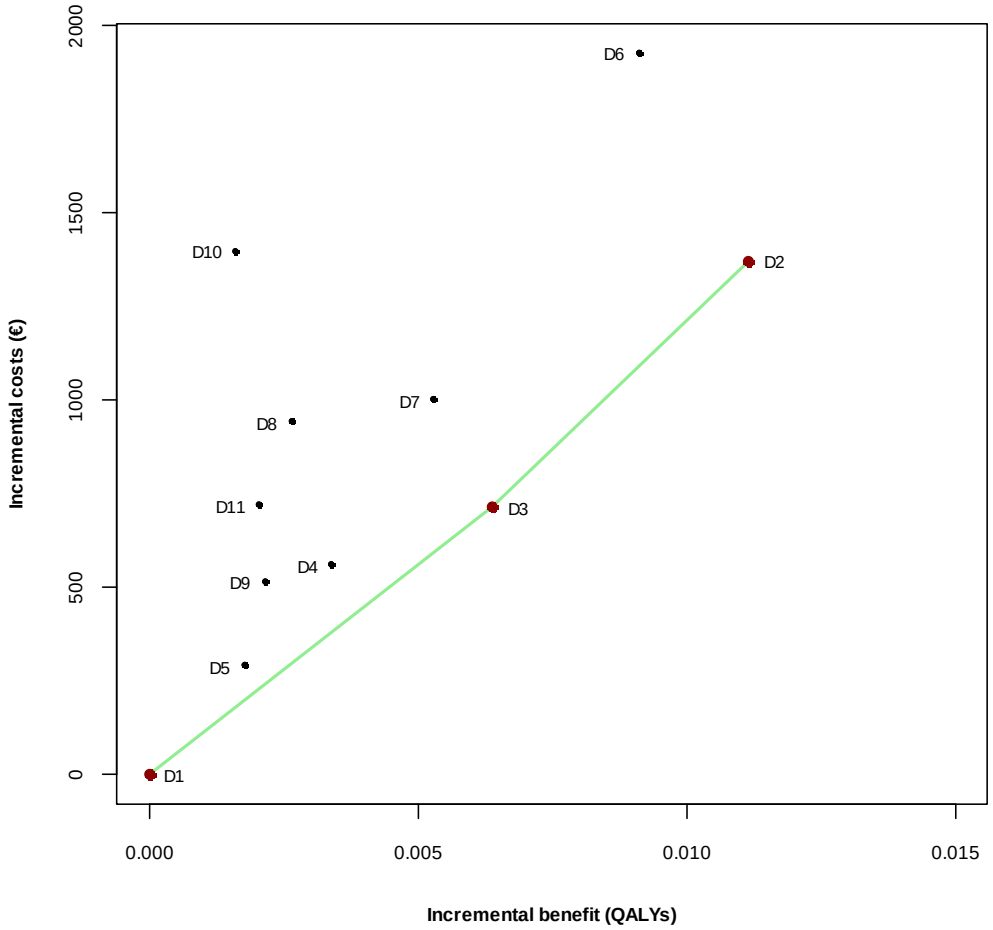
Strategy	Surveillance by age					Per person				Per 1,000 women*		
	20-24	25-29	30-34	35-39	40-49	QALYs	Cost	Screens	ICER	Screen-detected	Symptom-detected	BC mortality at 50
D02	None	None	None	None	MRI (12)	20.1718	2,613	9.8	122,858	58	95	9
D06	None	None	None	None	DMX+MRI (12)	20.1697	3,168	9.8	211,142	62	96	9
D03	None	None	None	None	MRI (24)	20.1670	1,956	4.9	111,649	47	106	10
D07	None	None	None	None	DMX+MRI (24)	20.1659	2,241	4.9	188,120	52	104	10
D04	None	None	None	None	DMX (12)	20.1640	1,800	9.8	163,553	39	119	10
D08	None	None	None	DMX (12)	DMX (12)	20.1633	2,183	14.7	352,955	51	110	10
D09	None	None	None	DMX (24)	DMX (24)	20.1628	1,756	7.9	238,280	36	121	10
D11	None	None	DMX (24)	DMX (24)	DMX (24)	20.1627	1,959	9.9	347,510	37	121	10
D05	None	None	None	None	DMX (24)	20.1624	1,533	4.9	162,659	26	129	10
D10	None	None	DMX (12)	DMX (12)	DMX (12)	20.1622	2,638	19.7	860,310	57	106	10
D01	None	None	None	None	None	20.1606	1,242	0.0	-	0	152	11

Abbreviations: DMX - digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging; QALYs – quality-adjusted life years; ICER – incremental cost-effectiveness ratio [relative to no surveillance]; BC – breast cancer.

** Estimated known population of women at high familial risk, but with no identified genetic mutations less than 50 years of age is 1,674 in Ireland.*

The cost-effectiveness plane of surveillance strategies for women with high familial risk is given below (Figure 5.10).

Figure 5.10 Cost-effectiveness plane for surveillance strategies for women with high familial risk, but no identified genetic mutations



As for the identified genetic mutation carrier subgroups, the cost-effectiveness frontier is defined by MRI-based strategies (Table 5.21).

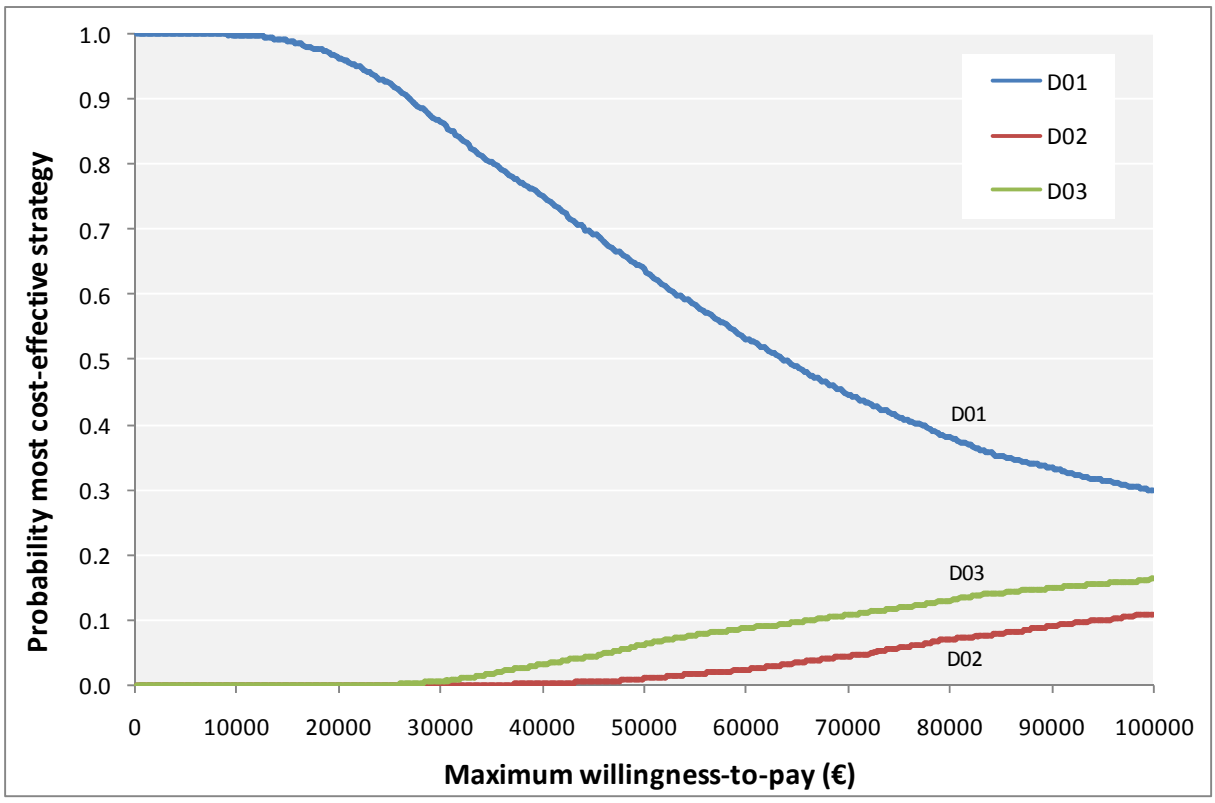
Table 5.21 ICERs for surveillance strategies for women with high familial risk but no identified genetic mutations

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER	Probability cost-effective	
						€20k/ QALY	€45k/ QALY
D01	20.1606	1,242	-	-	-	-	-
D03	20.1670	1,956	0.0064	714	111,649	0.00	0.10
D02	20.1718	2,613	0.0112	1,371	122,858	0.00	0.03

Note: ICER – incremental cost-effectiveness ratio relative to no surveillance (strategy D01). ICERs relative to next best strategy reported in Appendix 4.

The cost-effectiveness acceptability curves are presented in Figure 5.11. At all thresholds up to €100,000 per QALY, the 'no surveillance' strategy has the highest probability of being the most cost-effective.

Figure 5.11 Cost-effectiveness acceptability curves for surveillance strategies for women with high familial risk but no identified genetic mutations



Note: only strategies on the cost-effectiveness frontier are shown.

The five-year budget impact of 'no surveillance' is the least expensive option in terms of budget impact (Table 5.22). The surveillance strategies all fall within a €686,387 range from €898,115 to €1,584,502 for strategies D05 and D06, respectively. The incremental budget impact compared to no surveillance ranges from €134,624 for D05 to €821,011 for D06. The relatively large budget impact is due to the large size of the known population in this risk subgroup.

Table 5.22 Budget impact and resource use of surveillance for the known population of women with high familial risk, but no identified genetic mutations sorted by budget impact

Strategy	Surveillance by age					Resource use over five years					
	20-24	25-29	30-34	35-39	40-49	Budget impact (€)	False positives	DMX	MRI	Further testing	MR-guided biopsies
D01	None	None	None	None	None	763,491	0	0	11	36	0
D05	None	None	None	None	DMX (24)	898,115	28	633	21	68	1
D11	None	None	DMX (24)	DMX (24)	DMX (24)	931,463	39	867	23	79	1
D09	None	None	None	DMX (24)	DMX (24)	932,840	37	870	23	79	1
D04	None	None	None	None	DMX (12)	1,011,477	58	1,316	29	100	2
D08	None	None	None	DMX (12)	DMX (12)	1,065,517	72	1,629	33	115	2
D10	None	None	DMX (12)	DMX (12)	DMX (12)	1,090,895	80	1,804	36	122	2
D03	None	None	None	None	MRI (24)	1,092,299	56	0	662	98	20
D07	None	None	None	None	DMX+MRI (24)	1,190,635	82	633	671	125	28
D02	None	None	None	None	MRI (12)	1,380,628	115	0	1,364	160	39
D06	None	None	None	None	DMX+MRI (12)	1,584,502	168	1,317	1,380	213	55

Abbreviations: DMX - digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging.

5.4.4.1 Interpretation of results for the subgroup at high familial risk

At all thresholds up to €100,000, the no surveillance strategy has the highest probability of being the most cost-effective, i.e. none of the surveillance strategies including ad hoc surveillance constitute a cost-effective use of healthcare resources.

When compared to a strategy of no surveillance, the incremental cost-effectiveness ratios relative to no surveillance of the two strategies on the cost-effectiveness frontier are well in excess of the notional threshold of €45,000/QALY and would be considered not cost-effective. Ad hoc surveillance is ill-defined but presumed to be a mix of annual and biennial DMX from age 30 (D10 and D11), and no surveillance (D01). Both of the strategies on the frontier (D02 and D03) offer more health gain compared to ad hoc surveillance but only D03 (biannual MRI from age 40) does so at a lower cost.

To maximise health gain for this cohort of women for a given budget while at a minimum maintaining current effectiveness, D02 (annual MRI from age 40) is the optimal strategy (i.e. incremental budget impact of €617,137 over five years relative to no surveillance). Of note, given the large size of this cohort, known population 1,674 (95% CI: 1,241-2,326), in addition to concerns regarding non cost-effective use of resources and affordability, this strategy would generate 1,364 MRI and 39 MR-guided biopsies over five years posing a considerable challenge to the Health Service Executive (HSE) given the existing capacity limitations for these procedures. It may not be currently feasible to offer MRI-based surveillance to such a large cohort. As an alternative, annual digital mammography from age 40 to 49 (strategy D04) would be less costly and more effective than existing surveillance. However, it must be noted that in this cohort there is limited potential for mortality reduction and QALY gain compared to no surveillance.

5.4.5 Moderate risk subgroup

The known population of women aged less than 50 years at moderate risk was estimated to be 2,484 (95% CI: 1,718 to 3,614) (Table 5.2). The average number of QALYs per person is 20.24 for a strategy of 'no surveillance' (Table 5.23). Strategies of annual and biennial DMX from age 30 were included as these contribute to the estimate of current ad hoc surveillance. The most efficacious strategy was annual MRI surveillance from age 40 (E02) followed by combined annual DMX and MRI surveillance from age 40 (E06). The results for this cohort show the very modest reductions in mortality possible for any of the strategies evaluated compared to a strategy of no surveillance.

Table 5.23 Surveillance strategies for moderate risk sorted by effectiveness

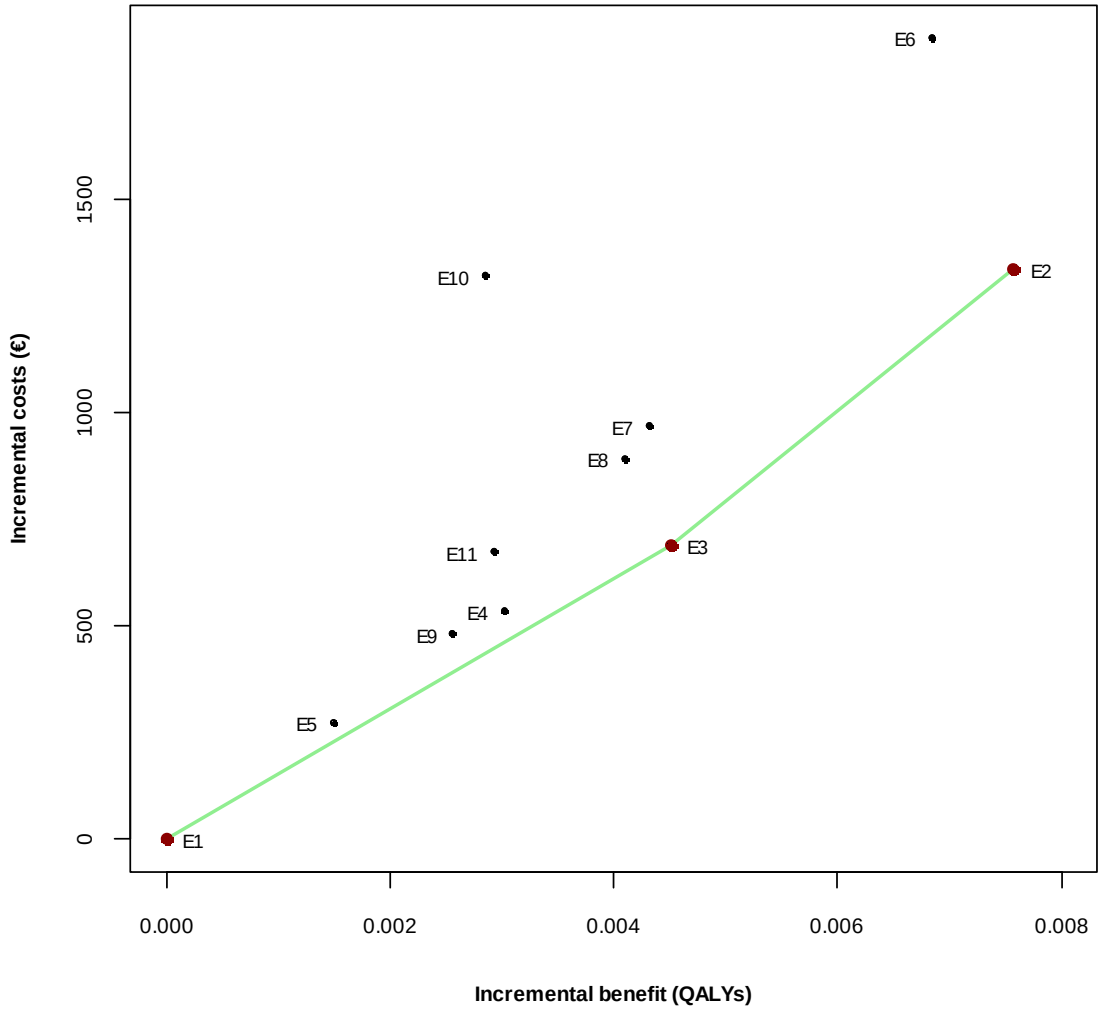
Strategy	Surveillance by age					Per person				Per 1,000 women*		
	20-24	25-29	30-34	35-39	40-49	QALYs	Cost	Screens	ICER	Screen-detected	Symptom-detected	BC mortality at 50
E02	None	None	None	None	MRI (12)	20.2439	1,807	9.8	176,516	23	31	4
E06	None	None	None	None	DMX+MRI (12)	20.2432	2,351	9.8	274,374	25	32	4
E03	None	None	None	None	MRI (24)	20.2409	1,160	4.9	153,012	18	36	4
E07	None	None	None	None	DMX+MRI (24)	20.2407	1,439	4.9	224,158	20	35	4
E08	None	None	None	DMX (12)	DMX (12)	20.2405	1,362	14.8	217,416	21	38	4
E04	None	None	None	None	DMX (12)	20.2394	1,003	9.8	175,818	16	41	5
E11	None	None	DMX (24)	DMX (24)	DMX (24)	20.2393	1,142	9.9	229,099	14	43	5
E10	None	None	DMX (12)	DMX (12)	DMX (12)	20.2392	1,791	19.8	462,263	23	37	4
E09	None	None	None	DMX (24)	DMX (24)	20.2389	949	7.9	186,716	14	42	5
E05	None	None	None	None	DMX (24)	20.2379	743	4.9	181,692	10	45	5
E01	None	None	None	None	None	20.2364	470	0.0	-	0	54	5

Abbreviations: DMX – digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging; QALYs – quality-adjusted life years; ICER – incremental cost-effectiveness ratio [relative to no surveillance]; BC – breast cancer.

** Estimated known population of women at moderate risk less than 50 years of age is 2,484 in Ireland.*

The cost-effectiveness plane of surveillance strategies for women at moderate risk is given below (Figure 5.12).

Figure 5.12 Cost-effectiveness plane for surveillance strategies for women at moderate risk



As for all of the other risk subgroups, the cost-effectiveness frontier is defined by MRI-based strategies (Table 5.24).

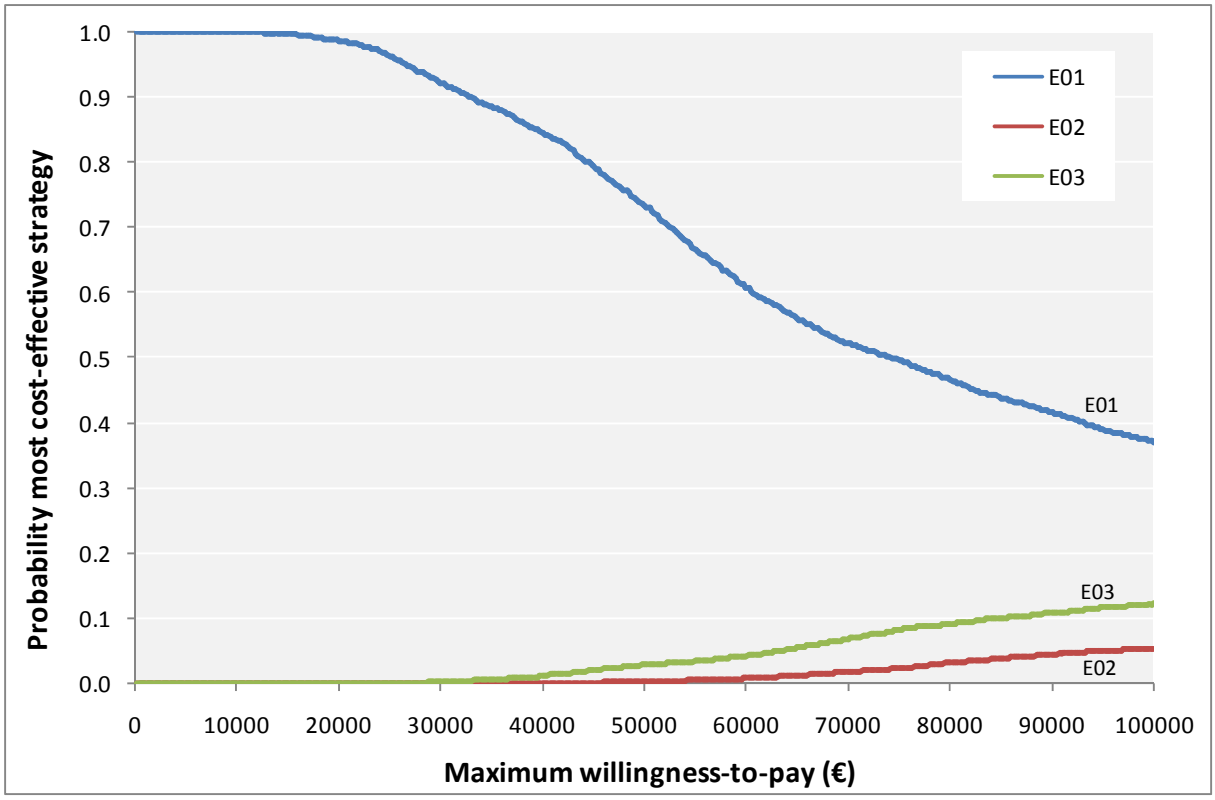
Table 5.24 ICERs for surveillance strategies for women at moderate risk

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER	Probability cost-effective	
						€20k/ QALY	€20k/ QALY
E01	20.2364	470	-	-	-	-	-
E03	20.2409	1,160	0.0045	689	153,012	0.00	0.05
E02	20.2439	1,807	0.0076	1,336	176,516	0.00	0.01

Note: ICER – incremental cost-effectiveness ratio relative to no surveillance (strategy E01). ICERs relative to next best strategy reported in Appendix 4.

The cost-effectiveness acceptability curves are presented in Figure 5.13. As for the high familial risk subgroup, the 'no surveillance' strategy has the highest probability of being the most effective at all thresholds up to €100,000 per QALY.

Figure 5.13 Cost-effectiveness acceptability curves for surveillance strategies for women at moderate risk



Note: only strategies on the cost-effectiveness frontier are shown.

As for all risk subgroups, the five-year budget impact of 'no surveillance' is the least expensive option in terms of budget impact (Table 5.25). The surveillance strategies all fall within a €939,354 range from €694,568 for strategy E05 to €1,633,922 for strategy E06. The incremental budget impact relative to no surveillance ranges from €160,679 to €1,100,033. The budget impact tends to be lower than for equivalent strategies in the high familial risk cohort. Although the known populations are of similar size, the lower risk of breast cancer in the moderate risk group entails lower treatment costs generated in this cohort.

Table 5.25 Budget impact and resource use of surveillance for other women at moderate risk sorted by budget impact

Strategy	Surveillance by age					Resource use over five years					
	20-24	25-29	30-34	35-39	40-49	Budget impact (€)	False positives	DMX	MRI	Further testing	MR-guided biopsies
E01	None	None	None	None	None	533,889	0	0	8	26	0
E05	None	None	None	None	DMX (24)	694,568	42	932	21	71	1
E09	None	None	None	DMX (24)	DMX (24)	743,500	56	1,283	25	85	1
E11	None	None	DMX (24)	DMX (24)	DMX (24)	744,696	58	1,274	25	87	1
E04	None	None	None	None	DMX (12)	845,241	86	1,939	33	116	2
E08	None	None	None	DMX (12)	DMX (12)	912,424	107	2,404	39	138	2
E03	None	None	None	None	MRI (24)	947,089	82	0	967	113	27
E10	None	None	DMX (12)	DMX (12)	DMX (12)	948,523	118	2,654	43	148	2
E07	None	None	None	None	DMX+MRI (24)	1,086,321	121	932	979	152	39
E02	None	None	None	None	MRI (12)	1,349,719	171	0	1,998	203	53
E06	None	None	None	None	DMX+MRI (12)	1,633,922	249	1,940	2,024	281	76

Abbreviations: DMX - digital mammography; DMX+MRI – combined DMX and MRI used at the same screen; MRI – magnetic resonance imaging.

5.4.5.1 Interpretation of results for the subgroup at moderate familial risk

At all thresholds up to €100,000, the no surveillance strategy has the highest probability of being the most cost-effective, i.e. none of the surveillance strategies including ad hoc surveillance constitute a cost-effective use of healthcare resources.

With ICERs in excess of €150,000/QALY compared to no surveillance, none of the surveillance strategies for moderate risk was cost-effective by usual standards. As for women with high familial risk, ad hoc surveillance is ill-defined but presumed to be a mix of annual and biennial DMX from age 30 (E10 and E11), and no surveillance (E01), weighted more towards strategies E11 and E01. Both of the strategies on the frontier (E02 and E03) offer more health gain compared to ad hoc surveillance but neither does so at a lower cost. Of the strategies using only DMX, E04 (annual DMX from age 40) and E08 (annual DMX from age 35) offer the potential for benefits, although the latter strategy does so at an increased cost. The possible breast cancer mortality reduction by age 50 is very limited for any of the strategies compared to no surveillance or ad hoc surveillance.

Compared to a strategy of no surveillance, the incremental cost-effectiveness ratios relative to no surveillance of the two strategies on the cost-effectiveness frontier (E02 [annual MRI from age 40] and E03 [biennial MRI from age 40]) are well in excess of the notional threshold of €45,000/QALY and would be considered not cost-effective. Both of the strategies on the frontier offer more health gain (increase in QALYs and a modest mortality reduction. As an alternative to an MRI-based strategy, annual DMX from age 40 would be of similar or lower cost than ad hoc surveillance but the gain in benefits is modest. Although not cost-effective, annual DMX from age 40 for women at moderate risk will be less costly and more effective than current ad hoc surveillance.

5.4.6 Budget impact of recommended strategies

The results of the economic analyses provide recommendations regarding suitable surveillance strategies for each risk subgroup. The budget impact of recommended and existing surveillance strategies are collated in Table 5.26 to compare the total cost and imaging requirements. The table shows an estimate of existing resource use along with estimates based on a purely cost-effectiveness point of view, where strategies are chosen from the frontier and should be cost-effective relative to no surveillance, and separately for pragmatic choices taking into account imaging logistics, the benefits relative to current ad hoc surveillance, and current international practice.

Table 5.26 Comparison of budget impact and main resource implications over five years for existing, the most cost-effective, and the proposed surveillance strategies by risk subgroup

Risk subgroup	Current practice					Cost-effectiveness perspective					Proposed surveillance				
	Strategy	BIA (€)	DMX	MRI	MR biopsy	Strategy	BIA (€)	DMX	MRI	MR-guided biopsy	Strategy	BIA (€)	DMX	MRI	MR-guided biopsy
BRCA1	A14/A15	355,292	163	182	8	A12	327,219	0	179	6	A13	348,537	124	181	7
BRCA2	B14/B15	217,928	118	131	5	B12	198,130	0	129	4	B13	213,660	90	130	5
Other high penetrance mutation carriers	C03	92,497	0	93	3	C03	92,497	0	93	3	C03	92,497	0	93	3
High familial risk but no identified genetic mutations	Ad hoc	1,060,261	1,629	34	2	D01	763,491	0	11	0	D04	1,011,477	1,316	29	2
Moderate	Ad hoc	874,726	2,164	37	2	E01	533,889	0	8	0	E04	845,241	1,939	33	2
Total		2,600,704	4,072	475	19		1,915,226	0	420	13		2,511,412	3,469	466	19
Incremental relative to no surveillance		907,945	4,072	450	19		222,467	0	395	13		818,653	3,469	441	19

Abbreviations: BIA – budget impact analysis; DMX - digital mammography; MRI – magnetic resonance imaging.

Strategies:

BRCA1 – A12, annual MRI from age 30; A13, annual MRI from age 30 combined with annual DMX from age 40; A14, annual MRI from age 30 combined with annual DMX from age 35; A15, annual MRI and DMX from age 30.

BRCA2 – B12, annual MRI from age 30; B13, annual MRI from age 30 combined with annual DMX from age 40; B14, annual MRI from age 30 combined with annual DMX from age 35; B15, annual MRI and DMX from age 30.

Other high penetrance mutation carriers – C03, annual MRI from age 20.

High familial risk but no identified genetic mutations – D01, no surveillance; D04, annual DMX from age 40.

Moderate risk – E01, no surveillance; E04, annual DMX from age 40.

It should be noted that the budget impact for other high penetrance mutation carriers includes both *TP53* and other mutations. However, the recommendation of annual MRI from age 20 only applies to those women with *TP53* mutations. Those who do not have a *TP53* mutation should receive the same surveillance strategy as the *BRCA1* and *BRCA2* subgroups. This will result in a reduced budget impact for the other high penetrance mutation carrier subgroup and an increased budget impact for the *BRCA1/BRCA2* subgroup. The overall effect is a net reduction in overall budget impact.

From a cost-effectiveness point of view, restricting choices to strategies on the cost-effectiveness frontier entails that surveillance for any risk group would be based on MRI alone or else no surveillance. This would result in no digital mammography beyond what is already used in symptomatic imaging, and a modest reduction of MRI usage from 475 to 420 over five years. The number of MR-guided biopsies would decrease from 19 to 13 over five years and the budget impact would decrease by €685,478 relative to existing ad hoc surveillance. As none of the surveillance strategies modelled for the high familial and moderate risk groups is cost-effective by traditional standards, these risk subgroups would receive no surveillance.

The alternative perspective allows for the provision of a digital mammography-based surveillance strategy for women at high familial risk with no identified genetic predisposition and those at moderate risk, in accordance with current international practice. Despite being not cost-effective relative to no surveillance, annual DMX from age 40 is less costly and more effective than existing ad hoc surveillance. The application of the recommended screening strategies will, over five years, lead to a €89,292 reduction in budget impact, 603 fewer digital mammograms, and nine fewer MRIs.

For women at high familial risk with no identified genetic mutations and at moderate risk, existing ad hoc screening reflected the definition given in Section 5.2.5 previously.

The BIA estimations were based on assumptions regarding the known population. However, as reported in Table 2.5, there may be a substantial population that are at elevated risk, but who are not known and therefore not presenting for surveillance at present. Should systematic surveillance be made available, it is possible that a greater proportion of the true population at elevated risk will become known to the services. In this event, the budget impact may increase substantially. The upper bound for the estimated number of known women with identified genetic mutations other than *TP53* (e.g. *BRCA1, BRCA2, Chek2*) was approximately 10% of the true population. Part of the reason for the magnitude of the underestimate is that the values are provided for *BRCA1* and *BRCA2* alone, as other genetic mutations are

included with the *TP53* subgroup. Hence the budget impact relating to that risk subgroup could increase 10-fold should complete ascertainment be achieved. For women with *TP53* mutations, the budget impact estimate of annual MRI from age 20 was based on all women with known high penetrance genetic mutations other than *BRCA1* and *BRCA2*. The modelled population was therefore approximately 80% of the true *TP53* population. For women at high familial risk with no identified genetic mutations, it was assumed that approximately 1,675 women are known at present, of which 1,042 are between the ages of 40 and 49 and hence eligible for the proposed surveillance strategy of annual DMX from age 40 to 49. The true population of women with high familial risk and no identified genetic mutations in this age group is estimated to be approximately 4,205, suggesting a potential four-fold increase in budget impact if full ascertainment was achieved. For women at moderate risk, the estimated known population is 2,484, of which approximately 2,272 are between the ages of 40 and 49 and therefore eligible for the proposed surveillance strategy. The true population of women at moderate risk aged 40 to 49 is approximately 16,379, which suggests a seven-fold increase in budget impact in the event of full ascertainment. It is difficult to determine the likelihood of increased ascertainment over a five-year horizon, particularly for women at moderate or high familial risk with no identified genetic mutations. Surveillance is already available to these subgroups on an ad hoc basis so a formalisation of surveillance may not attract many new women to attend clinics for risk assessment. Currently, there are significant capacity constraints in terms of genetic testing, thus the potential for large numbers to be identified in the next five years is limited. Any attempt to determine what level of ascertainment may be possible for any of the risk groups is therefore purely speculative.

It should be noted that, at present, an estimated 2,376 women aged less than 50 years classified (appropriately or inappropriately) as being at average risk are known to family risk clinics and some portion are receiving either annual or biennial digital mammography. It is not recommended that women at average risk receive surveillance. Discontinuation of surveillance of women aged less than 50 years at average risk will further reduce the overall budget impact and requirement for digital mammography compared to existing practice.

5.5 Scenario and sensitivity analyses

A number of scenario and sensitivity analyses were undertaken to test some of the assumptions about parameter values and to determine how sensitive the results were to changes in parameter values. Scenario analyses were undertaken in relation to two parameter sets, as the evidence supporting them could be questioned.

In accordance with the national guidelines,[125] univariate sensitivity analyses are presented to show how sensitive the results are to fluctuations in each parameter. Rather than carry out a sensitivity analysis on every strategy for every risk group, three strategies were chosen for analysis: annual MRI from age 40, annual mammography from age 40, and no surveillance. These strategies were tested in relation to the subgroup with high familial risk and no identified genetic mutations as this is a large subgroup where large uncertainty could have a significant impact on the budget impact. The strategies were chosen so as to isolate the two imaging modalities as well as investigating the situation with no surveillance. As the sensitivity analyses are specific to both the surveillance strategy and risk group, it is not possible to generalise the findings of the analysis to all strategies assessed in this report. However, the analysis is indicative of which parameters may contribute more to uncertainty in the model estimates.

5.5.1 Scenario analysis – diagnostic test accuracy of digital mammography

In the absence of evidence directly comparing surveillance MRI and digital mammography in women less than 50 years of age at elevated risk of breast cancer, the sensitivity and specificity of digital mammography was determined from a systematic review of diagnostic test accuracy studies of film mammography in women aged less than 65 years at elevated risk of developing breast cancer. While there is evidence to suggest that digital mammography outperforms film mammography in younger, average risk populations,[78] it is unclear if this advantage would extend to an elevated risk cohort. Given the discrepancy between the imaging technique and target population of the available studies and the present HTA, the EAG endorsed use of a conservative estimate of diagnostic test accuracy for digital mammography in the model as a pragmatic approach. However, other studies have used higher test accuracy in a similar context, so a scenario analysis was carried out whereby the sensitivity was increased from a median of 38% to 50%. To account for the typical negative correlation that exists between test sensitivity and specificity, the corresponding specificity values were decreased from a median 97% to 95%.

All of the surveillance strategies were re-evaluated using the increased sensitivity and decreased specificity for digital mammography. Across the five risk subgroups, there were 44 strategies out of the 70 evaluated that included digital mammography, either on its own or in combination with MRI. The increased sensitivity used in the scenario analysis resulted in higher QALYs per person and increased costs associated with the reduced specificity which results in increased false positives.

For strategies involving digital mammography, the ICERs relative to no surveillance were typically lower when the higher sensitivity was used. The reduction in ICERs was generally below 5%. The instances where the ICER reduction was larger applied

to strategies for women a high familial risk with no identified genetic mutations and the moderate risk group. The reductions were most pronounced in the strategies that involved annual and biennial digital mammography from the age of 30, where the ICERs were almost halved. For some strategies involving digital mammography, there was the potential for an increased mortality reduction, although generally this was one fewer death per 1,000 women, and was reflected in the increased QALYs.

The reductions in ICERs were not sufficient to bring these strategies onto the cost-effectiveness frontier for any of the risk subgroups, and hence the interpretation of results would not be changed if the higher sensitivity was used in the model for digital mammography.

5.5.2 Scenario analysis – proportion of patients receiving each type of treatment

The proportion of patients receiving each type of treatment by stage at diagnosis was estimated from a variety of data sources. The largest source of data was from the National Cancer Registry Ireland (NCRI), which collects data on all cancer cases in Ireland. Data include surgical, radiation therapy and chemotherapy interventions with corresponding ICD-10AM codes. Due in part to a lack of specificity in some of the codes used, it was not always possible to be certain that a code pertained to one of the seven treatments used in generating treatment costs: chemotherapy; radiotherapy; mastectomy; wide local excision; sentinel node biopsy; axillary clearance; and endocrine treatment. Alternative proportions were suggested by treating physician members of the EAG, based on assumptions about typical treatment pathways. For the main analysis, assumptions about treatment proportions were generated using NCRI data adjusted by treating physicians (who were members of the EAG) according to recommended clinical practice. To test whether using the EAG assumptions altered the results, a scenario analysis was undertaken where the surveillance strategies for all risk subgroups were re-evaluated using treatment proportions calculated from a combination of the NCRI data, the EAG assumptions, and three local hospital datasets.

Using the composite values resulted in total treatment costs that were, on average, 7.9% (range: 3.9% to 12.7%) greater than those generated using the data from the main model. The largest increases occurred in the no surveillance strategies. With costs increased, one could anticipate that cost-effectiveness might be reduced. However, as the cost increases also applied to the comparator of no surveillance, the ICERs based on the EAG values were on average 1.2% (range: -0.7% to 2.9%) lower than calculated in the main model. There was an almost perfect correlation between the ICERs generated using the two different assumptions about treatment proportions. The alternative values also had no impact on which strategies were included in the cost-effectiveness frontier for any of the risk subgroups.

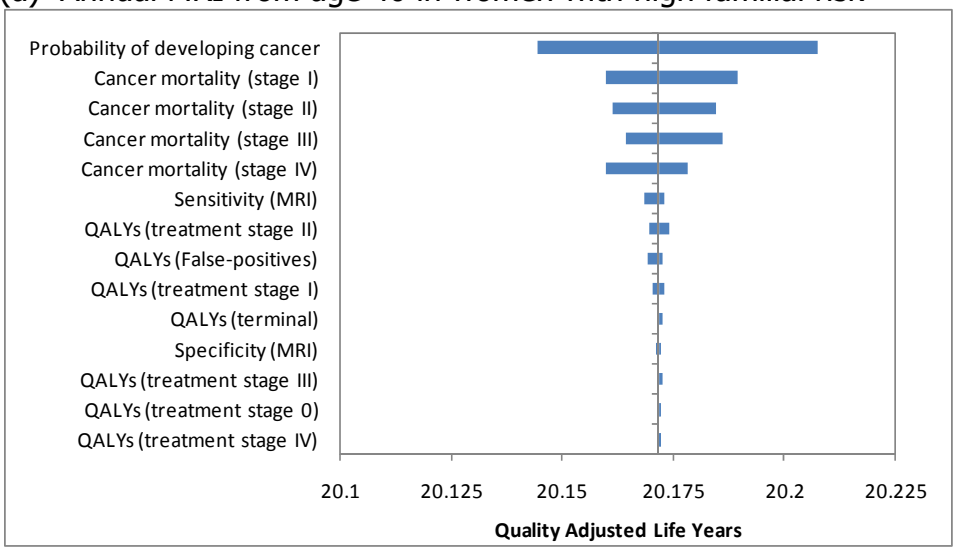
Interpretation of the analysis is therefore not affected by the assumptions around treatment proportions.

5.5.3 Univariate sensitivity analysis: QALYs per person

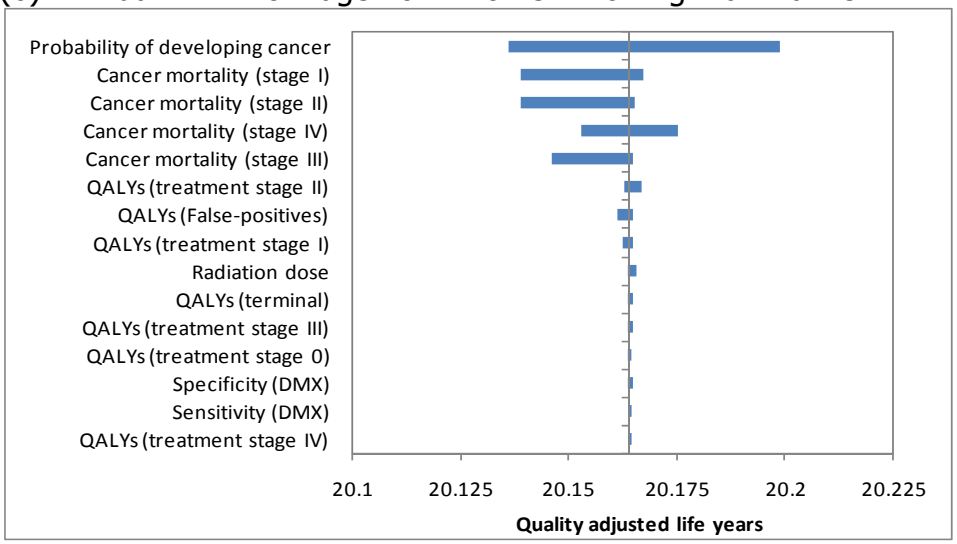
For the analysis of QALYs per person, cost elements had no impact on the estimated number of QALYs. The tornado diagrams are presented in Figure 5.14. For all three strategies, variation in the probability of developing breast cancer is the most influential parameter affecting the estimated QALYs per person, causing a fluctuation of approximately ±0.03 QALYs per person. This is perhaps not surprising as the probability dictates how many women will develop breast cancer (and hence how many will require treatment), and how many are likely to have premature death due to breast cancer. The next most important parameters are the mortality associated with breast cancer at each stage at diagnosis.

Figure 5.14 One-way sensitivity analysis: QALYs per person for selected strategies

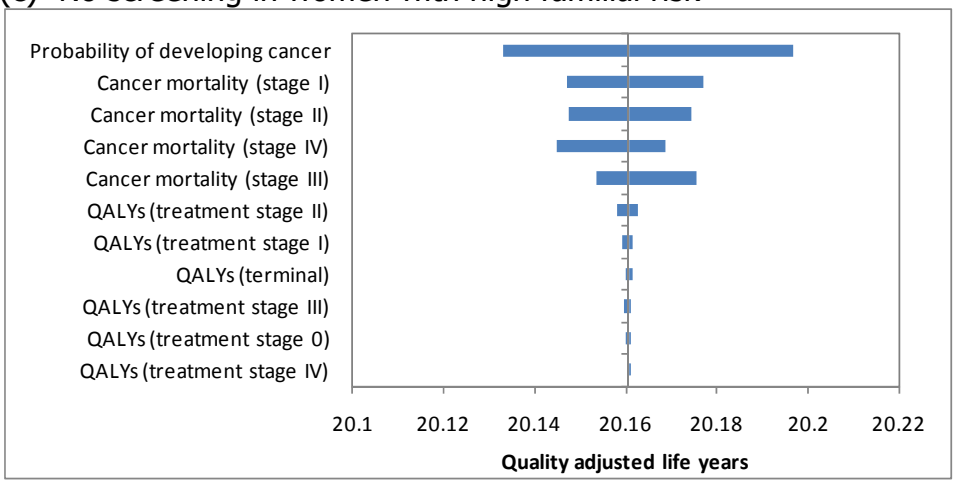
(a) Annual MRI from age 40 in women with high familial risk



(b) Annual DMX from age 40 in women with high familial risk



(c) No screening in women with high familial risk



The QALYs lost due to false positives have a greater impact in the MRI-based strategy than in the other two strategies tested, due to the lower specificity of MRI testing, but the impact was modest. The impact of radiation dose is important in digital mammography due to the extent to which it induces cancers which then require treatment and have an associated mortality rate, but is negligible compared to the more influential parameters of developing cancer and the associated mortality rates. The uncertainty around treatment disutility has limited influence on the overall estimate of QALYs per person in any of the strategies investigated, causing a fluctuation of approximately ±0.001 QALYs per person.

5.5.4 Univariate sensitivity analysis: cost per person

For the analysis of costs per person, the main parameters included were those relating to surveillance and treatment costs. The tornado diagrams are presented in Figure 5.15 below. For all three strategies, variation in the probability of developing breast cancer is the most influential parameter affecting the estimated cost per person.

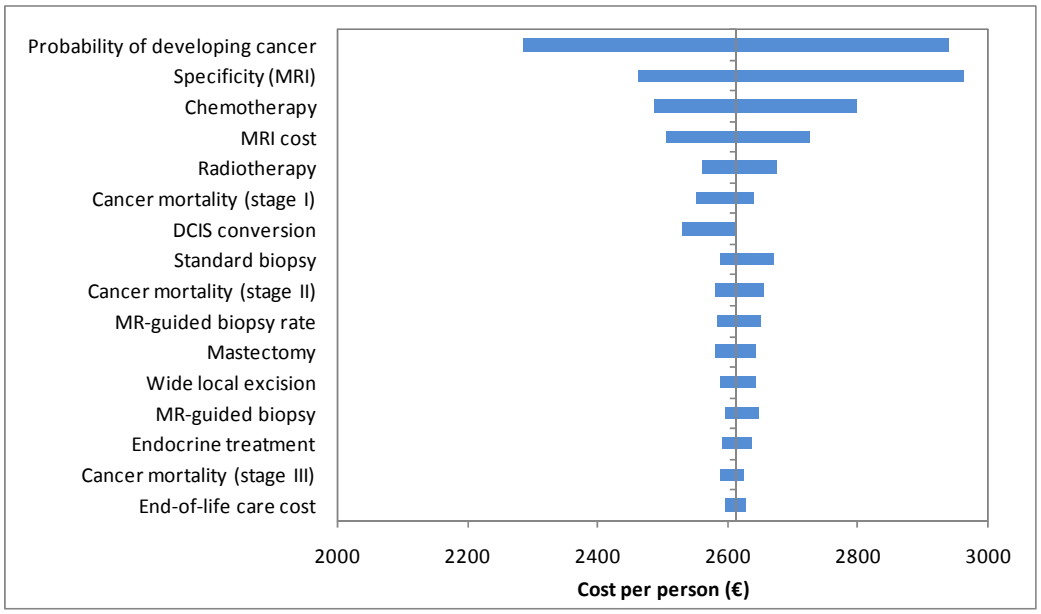
For MRI surveillance, uncertainty in the specificity of MRI imaging was the second most influential parameter. The specificity was varied between 80% and 96%, which resulted in the cost per person varying between €2,461 and €2,962 (with the higher cost associated with a lower specificity). The importance of specificity relates to the volume of false positives and the associated costs due to the further testing required.

For digital mammography surveillance, as with MRI, uncertainty around the test specificity had a noticeable effect on the estimate of costs. The range for specificity (87% to 98%) was similar to that for MRI, but the impact on the cost per person was less pronounced (€1,772 to €2,002). The narrower range is because the further testing associated with mammography is less likely to involve an MR-guided biopsy and hence is on average less expensive than further testing following MRI surveillance.

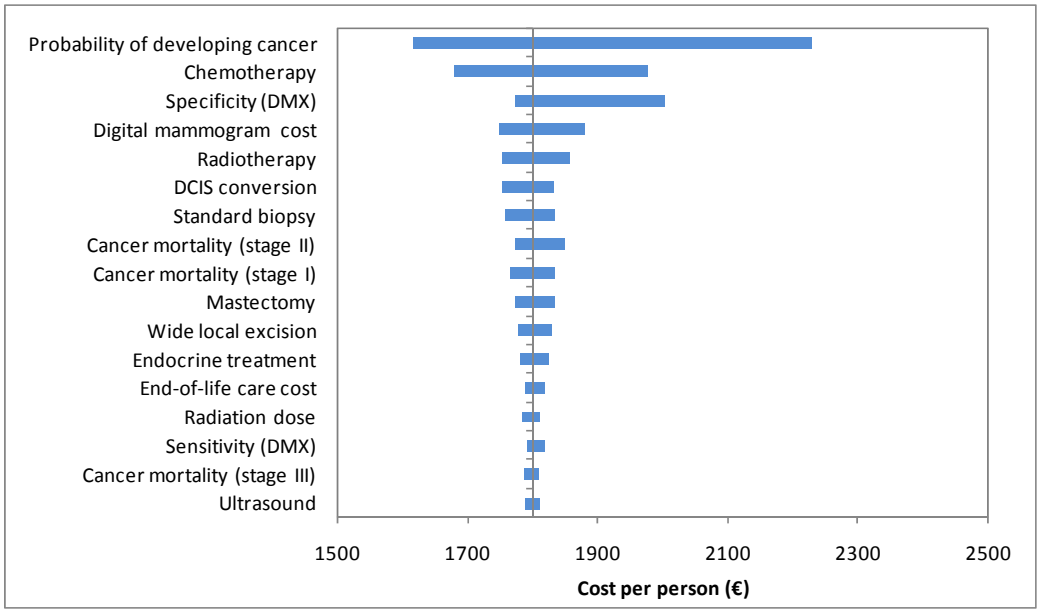
In the no surveillance strategy, the estimate of cost is most affected by uncertainty in the probability of developing cancer, followed by the cost of chemotherapy and radiotherapy.

Figure 5.15 One-way sensitivity analysis: cost per person for selected strategies

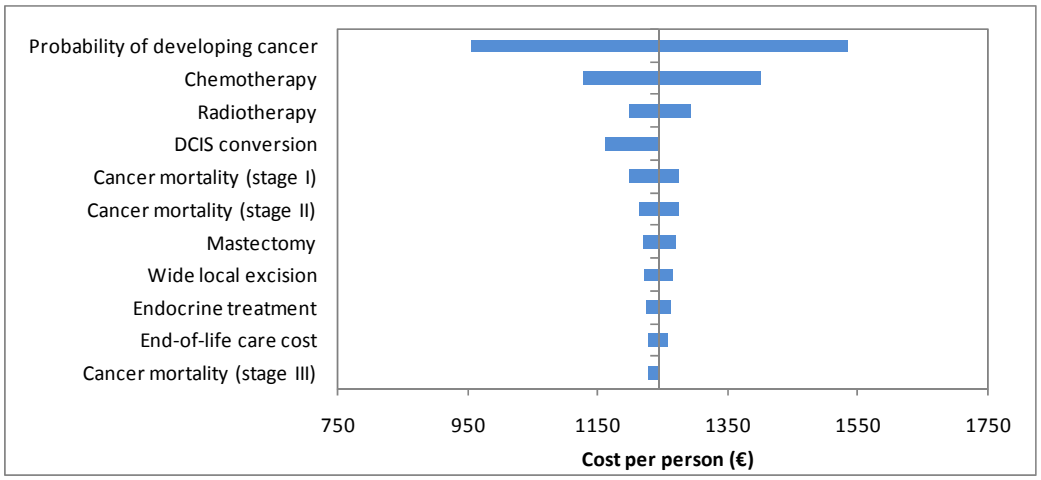
(a) Annual MRI from age 40 in women with high familial risk



(b) Annual DMX from age 40 in women with high familial risk



(c) No screening in women with high familial risk



Note: only parameters giving rise to a greater than 1% fluctuation in cost per patient are included in the tornado plots.

5.5.5 Univariate sensitivity analysis: five-year budget impact

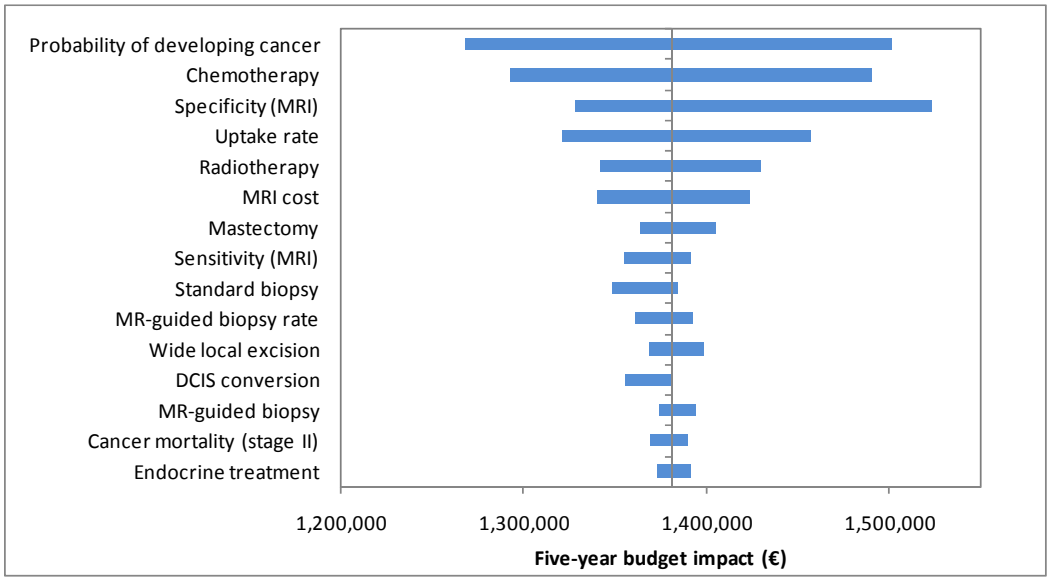
For the analysis of five-year budget impact, additional parameters were included such as the rate of prophylactic surgery and pregnancy. The tornado diagrams are presented in Figure 5.16.

For all three strategies, variation in the cost of chemotherapy and the probability of developing cancer are major contributors to uncertainty in the estimate of budget impact. For the screening strategies investigated, variation in the uptake rate is also an important contributor to overall uncertainty. The estimates of uptake rates used in the model were derived from an elevated risk population with small numbers giving rise to substantial uncertainty in younger members of the cohort. It is possible that uptake rates might be higher among the very high risk mutation carriers.

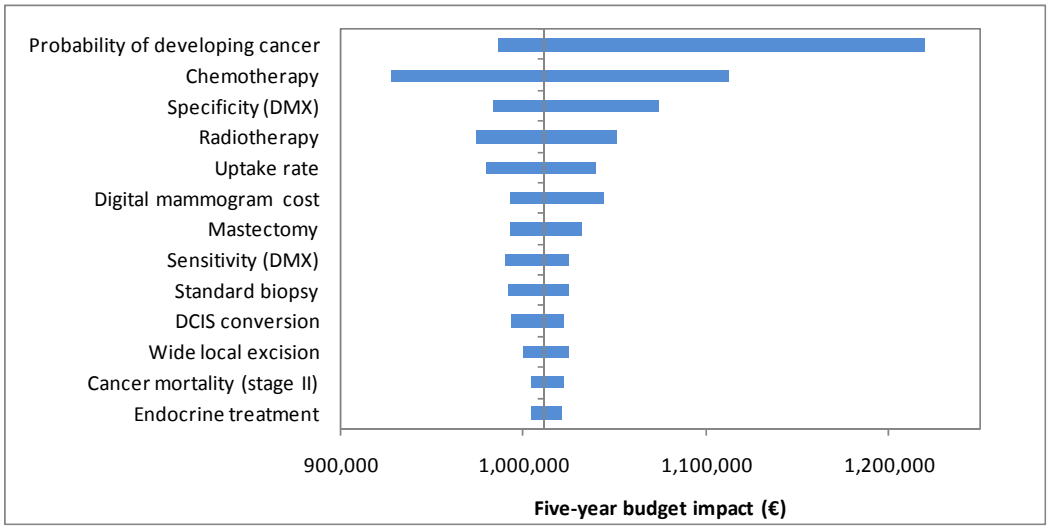
The uncertainty in the estimates of budget impact of both MRI and digital mammography surveillance are also affected by uncertainty in the diagnostic test accuracy of the imaging, particularly the specificity which dictates the rate of false positives and impacts on the amount of further testing.

Figure 5.16 One-way sensitivity analysis: budget impact for selected strategies

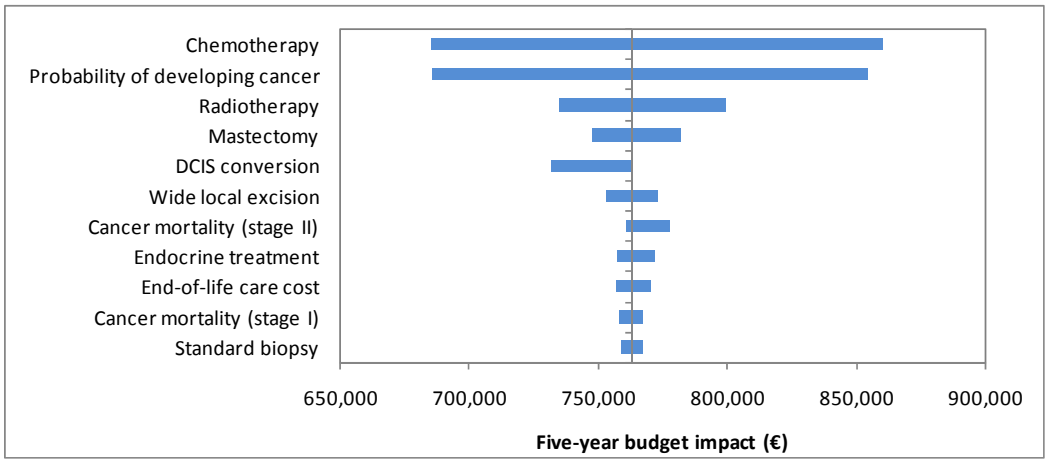
(a) Annual MRI from age 30 in women with high familial risk



(b) Annual DMX from age 30 in women with high familial risk



(c) No screening in women with high familial risk

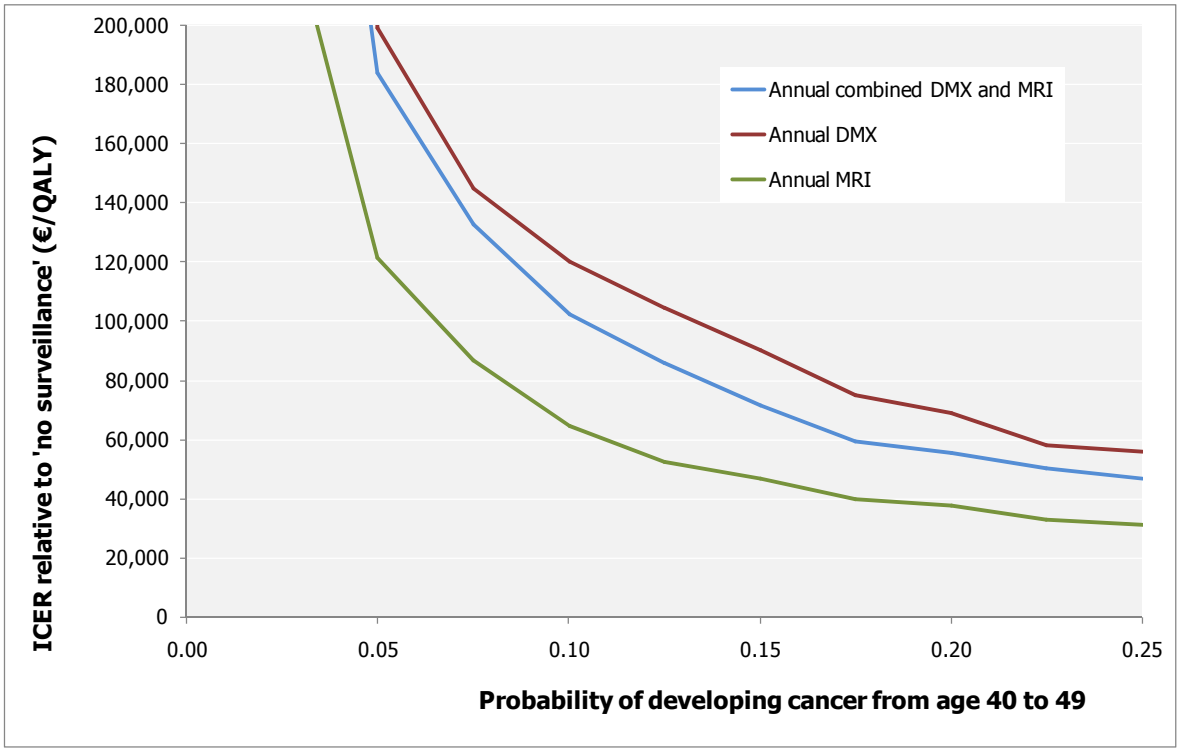


Note: only parameters giving rise to a greater than 1% fluctuation in budget impact are included in the tornado plots.

5.5.6 Ten-year risk of developing breast cancer and ICERs

It is clear that the incremental cost-effectiveness ratios (ICERs) are strongly influenced by the underlying risk of breast cancer developing in the women undergoing surveillance. To determine the relationship between risk and incremental cost-effectiveness, a scenario analysis was undertaken. Ten-year risk from age 40 to 49 was varied from 1% to 25%. This was achieved by using the risk profile for women with a *BRCA1* mutation and varying the total risk using a power function. The model was run for the range of 10-year risk values for three strategies: annual digital mammography; annual MRI; and annual combined digital mammography and MRI, all from age 40 to 49. The no surveillance option was also evaluated for each 10-year risk value in order to calculate the ICERs relative to no surveillance. At all risk values, MRI is the most cost-effective (Figure 5.17), with digital mammography and combined digital mammography and MRI having similar cost-effectiveness results. The average, moderate and high risk groups are defined according to 10-year breast cancer risks of less than 3%, between 3% and 8%, and greater than 8%, respectively.

Figure 5.17 Cost-effectiveness of surveillance from age 40 to 49 for a range of 10-year breast cancer risk values



5.6 Limitations of the economic model

5.6.1 Assumptions

Any economic model is necessarily a simplification of a real-world experience, and hence a range of assumptions is made to enable development of a model. The model developed for the present HTA follows a cohort of women from age 20 to life expectancy using a Markov model. A natural history model would have been preferable as it would have allowed for the modelling of disease progression to mimic what happens in reality. Such a modelling approach requires large amounts of data regarding sojourn times and diagnostic test accuracy as a function of tumour size and the woman's age. Use of such data requires extensive data collection and also detailed model calibration and validation. Such a modelling approach was beyond the scope of this HTA due to the limited data available and concerns over its appropriateness.

In the modelling approach used, every attempt was made to pair simulations so that results could be compared across strategies, not just at a summary level, but also at an individual simulation level. This was achieved by setting random seeds throughout the code. However, some random variation still occurred so that perfect pairing was

not possible. The impact of such variation should be negated by the use of many sampled cohorts.

Survival is estimated at diagnosis and hence is a function of age at diagnosis and stage at diagnosis. It is noted from NCRI data that average survival for stage III breast cancer is higher in 40-49 year old women than for 30-39 year olds. Hence, in the model a screen-detected stage III case at 39 years is less likely to survive than if they were symptom-detected and stage III at age 40. Although a symptom-detected case is more likely to have a later stage at diagnosis, there is still the potential for anomalous results. Again such inconsistencies should have limited impact due to the large number of sampled cohorts.

The magnitude of mortality reduction appears quite high in some cases, particularly relative to published assumptions of a 15% to 25% reduction due to surveillance. Two points should be borne in mind when interpreting these data. Firstly, the estimates from the cost-effectiveness model assume perfect uptake of surveillance with no surveillance rounds missed due to pregnancy or a voluntary decision not to participate. Relative to no surveillance, this will estimate greater effectiveness than would be seen in practice. Secondly, a situation with absolutely no surveillance is unlikely to arise in reality for women at elevated risk. Women who know themselves to be at high risk may have a lower threshold for seeking medical advice regarding any perceived problems and hence may have better prospects of early detection.

A core assumption of the models used in this analysis is that women are correctly classified to risk category. That is, women modelled as *BRCA1* have an annual risk of developing breast cancer associated with *BRCA1* mutation carriers. In reality, there is likely to be some degree of misclassification, which can arise for a variety of reasons. This will particularly affect women waiting for genetic testing, who may be conservatively assigned to a higher risk status pending the results of testing. If they test negative, they may be reclassified to a lower risk group. For women in moderate risk or high familial risk with no identified genetic predisposition, the quality of the classification can be impacted by the quality of the family history recording. Women that are wrongly classified will receive surveillance that will not be optimal for their true risk, which could entail over- or under-surveillance. Over-surveillance can lead to unnecessary radiation exposure and resource usage, while under-surveillance will potentially lead to later detection of cancers with the consequence of poorer outcomes. Hence the results of the models must be interpreted in the context of correct classification.

5.6.2 Availability, robustness and quality of data to populate the model

The accuracy of the outputs from the economic model depends on both the accuracy of the input parameters and the manner in which the model combines those

parameters. Data on the diagnostic test accuracy was obtained from international studies, but due to the limited evidence there was considerable uncertainty around the estimates of sensitivity and specificity. Furthermore, there is evidence to suggest that digital mammography in women aged less than 50 years has a poor sensitivity for invasive cancers, but a relatively high sensitivity for DCIS, whereas the opposite applies to MRI. The values used in this analysis are based on an average across DCIS and invasive cancers. Using the assumption that rates of DCIS should be comparable between Irish and non-Irish populations of women aged less than 50 at elevated risk, then the average sensitivity should be similar. The important distinction is that the early detection of DCIS may not yield the same health benefits as early detection of invasive cancer. Hence the use of an average sensitivity may, in this case, overstate the benefits derived from digital mammography and understate the benefits of MRI. No data were collected on the diagnostic test accuracy of further testing given to women who return a positive surveillance test. Although a small percentage will return a false negative from further testing, this is not a function of the surveillance strategies and hence should not affect the relative differences between strategies.

The diagnostic test accuracy of digital mammography is linked to breast tissue density and is generally much higher in post-menopausal women. It is probable that test sensitivity improves with age, particularly for women in their 40s and 50s. In the absence of any firm evidence regarding the target population, it was not possible to generate a plausible gradient of increasing test sensitivity with age. Had this been incorporated into the model, strategies involving digital mammography in women 40 years and over would have been estimated to be more effective than has been reported in this study. The converse is that, as the sensitivity values used represent an average, the test accuracy would be decreased for younger women and hence strategies using digital mammography in women aged less than 40 would have had a reduced effectiveness.

The population of women in each risk group that currently presents at high risk clinics is not recorded centrally. The estimates used in this report were obtained by inference using a variety of data sources and expert opinion. Data from a family risk clinic were used to determine the frequency of screening mammograms for women at moderate and high familial risk, and these rates were applied to the estimated known numbers of women to calculate the number of screening mammograms annually. Using data reported by hospitals and estimated by the NCCP, it was possible to test the plausibility of the estimates based on the known number of screening mammograms carried out in women aged less than 50. The figures obtained for the number of screening mammograms were broadly similar suggesting that the population estimates used in the model are accurate, if imprecise.

A number of the epidemiological parameters, such as survival and stage at diagnosis, were obtained from national data for women aged less than 50 with breast cancer. These data represent a cohort that is a mix of women at average, moderate and high risk of developing breast cancer. While the women at moderate and high risk will be over-represented in these data given their elevated risk of developing breast cancer, the data may not fully reflect the survival and stage at diagnosis in women at elevated risk. Women at high risk tend to have more aggressive tumours and hence tend to present with a higher stage at diagnosis and may also have a lower survival rate than women at average risk presenting at an equivalent stage.

5.7 Summary

An economic model was presented in this chapter that was used to determine the cost-effectiveness of different surveillance strategies for women at elevated risk of developing breast cancer. The parameters used in the model were derived from a wide variety of sources, some of which were used as proxies in the absence of data on the specific risk groups being analysed.

For all risk subgroups, MRI offers the most effective approach to surveillance in terms of increased QALYs per person and reductions in breast cancer mortality, but at an increased cost. With the exception of a strategy of no surveillance, digital mammography alone results in the fewest QALYs per person, and the highest breast cancer mortality. The limited effect of digital mammography is due to a combination of poor test sensitivity in women aged less than 50 years and the increased incidence of cancer from radiation exposure.

For women with identified high penetrance genetic mutations (e.g. *BRCA1*, *BRCA2*, *TP53*), existing ad hoc surveillance is effective, but further mortality reductions are possible. However, given the small size of these cohorts, the reductions will be very small in absolute terms. The risk subgroup of 'other high penetrance genetic mutations' used in this study amalgamated *TP53* with other mutations. However, it is evident from the literature that *TP53* mutation carriers have a very high lifetime risk, with a significant risk occurring before the age of 30. When assessing the results of strategies for carriers of other high penetrance genetic mutations, it must be borne in mind that an early start age for surveillance benefits the *TP53* subgroup, but may not be advisable for the women with other identified high penetrance genetic mutations in that risk subgroup. For women with *BRCA1* and *BRCA2* mutations, the additional costs and impact on cost-effectiveness of commencing MRI surveillance earlier, such as at age 25, are small. However, in a limited number of individual cases it may be suitable to commence surveillance earlier than age 30 when deemed appropriate given an individual's family history and context.

For women with high familial risk, but no identified high penetrance genetic mutations, the estimated current ad hoc surveillance is neither effective nor efficient, while the scope for breast cancer mortality reduction at age 50 is very limited in this cohort.

For women at moderate risk, the existing ad hoc surveillance was found to be moderately more effective than no surveillance, but the scope for mortality reductions or increases in QALYs is extremely limited in this cohort.

Uncertainty in the probability of developing cancer plays a significant role in the uncertainty in the estimates of costs and benefits. In this study, the various risk subgroups are treated as homogeneous in terms of cancer risk, although in reality there is much variation within subgroups. The results are presented under the assumption of an 'on average' benefit and cost, with the understanding that those at lower risk within a subgroup will benefit less and those at higher risk will benefit more.

There was some difficulty in determining the cost of imaging in the Irish healthcare system. From the univariate sensitivity analysis, it is clear that variation in the estimate of MRI cost has a major impact on the estimate of the cost of an MRI-based surveillance strategy.

5.8 Key messages

- For women aged less than 50 years with identified high penetrance genetic mutations, standardised surveillance offers a significant opportunity to reduce mortality. Annual MRI from age 30 to 49 is the recommended strategy for those with *BRCA1* and *BRCA2* mutations. The addition of annual digital mammography from age 40 to 49 could be offered to maintain accordance with current international practice although this is more costly and unlikely to result in a substantial clinical benefit. For women with an identified *TP53* mutation, annual MRI surveillance from age 20 to 49 is the recommended strategy.
- For women at high familial risk with no identified genetic mutations, surveillance before the age of 40 is not recommended on the basis of cost or clinical effectiveness. While surveillance from age 40 to 49 is not cost-effective compared to no surveillance, providing annual MRI-based surveillance is less costly than existing ad hoc surveillance and offers the potential of a minor mortality reduction. If it is considered impractical to offer MRI-based surveillance to such a large cohort, but offering some form of standardised surveillance is considered desirable, then annual digital mammography from age 40 to 49, in accordance with current international practice, would be less costly and more effective than existing surveillance.

- For women at moderate risk, surveillance before the age of 40 is not recommended on the basis of cost or clinical effectiveness. Similar to women with high familial risk, surveillance is not cost-effective from ages 40 to 49 compared to no surveillance. However, providing annual MRI-based surveillance is less costly than existing ad hoc surveillance and offers the potential of a minor mortality reduction. If it is considered impractical to offer MRI-based surveillance to such a large cohort, but offering some form of standardised surveillance is considered desirable, then annual digital mammography from age 40 to 49 would be less costly and more effective than existing surveillance.
- In exceptional individual cases, it may be appropriate to commence surveillance at an earlier age than for the risk group generally given the individual's particular family history and context.
- The known population of women aged less than 50 who are carriers of high penetrance genetic mutations is relatively small. As a consequence, the incremental budget impact of different surveillance strategies for this cohort tends to be small. However, the small size of the cohort means that potential mortality reductions are small in absolute terms.
- Compared to current ad hoc surveillance, selecting surveillance strategies based on cost-effectiveness will, over five years, lead to a €685,478 reduction in budget impact, 4,074 fewer digital mammograms, 55 fewer MRIs, and no substantive change in MR-guided biopsies.
- Compared to current ad hoc surveillance, selecting surveillance strategies that maximise health gain for a given budget while maintaining current effectiveness will lead to a €89,292 reduction in budget impact, 603 fewer digital mammograms, and no substantive change in MRIs over five years.
- The budget impact estimates are directly proportional to the identified population. A 10% increase in the identified population will lead to a 10% increase in the budget impact.
- The cancer risk varies within subgroups such that a strategy that is not, on average, cost-effective for a subgroup, may be cost-effective for some women within that subgroup. (This may be reflected in the current approach to surveillance.)
- The uncertainty in the results of the model was primarily driven by uncertainty in the probability of developing cancer, the cost of imaging, and the diagnostic test accuracy. The probability of developing cancer was estimated from international studies. Very limited data are available on diagnostic test accuracy specific to women aged less than 50 at elevated risk of developing breast cancer. Sensitivity and scenario analyses were used to test the impact of assumptions and found that interpretation of the results is unchanged.

6 Ethical considerations

6.1 Introduction

One of the ethical challenges in healthcare distribution is to obtain a balance between the expectations of individual patients and a fair distribution of resources to allow for the best medical outcomes for the greatest number of people. The specific remit of this HTA is to assess surveillance using mammography, MRI or a combination thereof in women aged less than 50 years that are known to be at elevated risk of developing breast cancer due to a genetic predisposition or a strong family history. Surveillance is termed a secondary preventive measure which aims to detect breast cancer at the earliest possible stage to reduce the rate of breast cancer death. International guidelines recommend that routine surveillance should be offered to women in this category, however, there is no consensus currently regarding the optimal design of a surveillance programme.[7;49;143-146]

The framework report developed by the Expert Advisory Group on Hereditary Cancer Risk and the associated cohort of women identified as being at elevated risk are used as the basis to this HTA.[3] The framework outlines the agreed definitions of 'moderate' and 'high' risk, the standardised risk assessment model to be used across family risk clinics in Ireland, and the referral pathways for those at risk. Surveillance here, therefore, refers to monitoring women known to be at elevated risk of developing breast cancer. Ad hoc surveillance is currently offered to this cohort to a variable extent at a local and regional level, but is not universally available. As such, the issues specifically relevant in this HTA are the ethical and social issues for the provision of an organised surveillance programme for these women.

It is acknowledged that there are others at elevated risk of breast cancer for whom surveillance is also indicated. This includes women with an iatrogenic risk of breast cancer secondary to therapeutic chest radiation at a young age for Hodgkin Lymphoma or other paediatric and young-adult cancers. While not included within the remit of this report, it is recommended that consideration should be given to the specific management of these individuals should a national breast cancer surveillance programme be established.

6.2 Ethics of breast cancer surveillance

Ethical considerations relevant to a cancer screening programme were reported in a previous HTA of colorectal cancer screening.[121] These considerations and their

relevance to this HTA are discussed below. The EUnetHTA[‡] core HTA model for screening technologies was used to identify any further relevant ethical issues.[(147)] The main issues identified are informed consent (particularly regarding the benefits versus risks of surveillance), equity of access and allocation of resources.

Autonomy and respect for personal choice, informed consent and the risks versus benefits of surveillance[(121;147)]

In a medical context, respect for a person's autonomy is considered a fundamental ethical principle. Autonomy can be defined as the ability of the person to make his or her own decisions. Every adult with decision-making capacity is entitled to choose whether to accept or refuse an intervention, to obtain a second opinion or choose alternative treatment. In the process of obtaining informed consent, all individuals should be treated equally, however, additional time or support may be required for those with impaired decision-making capacity. A person's decision must be based on having received sufficient information to enable him or her to understand the nature, potential risks and benefits of the proposed intervention. Restricting a person's choice, in terms of the availability, type and frequency of care, could be considered an infringement on their right to respect for their personal autonomy. However, it should be noted that this right, particularly in the healthcare setting, is not absolute. Healthcare budgets are finite and an individual's right to choose surveillance or the location at which this service is provided to them may conflict with other values or priorities, such the need to benefit the wider community.

In the specific context of breast cancer surveillance, the woman must receive sufficient information to enable her to understand the benefits and risks associated with surveillance, including the potential for negative effects such as the possibility of misdiagnosis or overdiagnosis, and to understand the alternatives to surveillance. For example, as discussed in Chapter 4, breast MRI surveillance is associated with a higher rate of 'false-positive findings' (where a healthy individual is incorrectly identified as having the condition) than digital mammography. It is documented that false-positive test results may give rise to unnecessary distress and worry for the individual.[(45;147)] For women at elevated risk of breast cancer, a false-positive result may cause a disproportional reaction as they are less likely to draw solace from assurances that the majority of those recalled for further assessment will not have cancer. A false-positive surveillance test result may also result in further investigations being carried out on an otherwise healthy individual.[(147)] Alternatively, false-negative results (individual incorrectly identified as being healthy) may give false security and ultimately delay an accurate diagnosis, with potentially fatal

[‡] European collaboration that consists of government-appointed organisations, national and regional agencies and non-for-profit organisations that produce or contribute to HTA.

consequences. As noted, in chapter 3.4, the potential for false-negative test results is a recognised and accepted part of even optimal surveillance programmes,[45] and therefore this fact should also be addressed in the informed consent process.

The safety, risks and benefits of mammography and breast MRI have been discussed in detail in Chapter 3. In particular, the risk of toxicity due to cumulative radiation exposure from repeated mammography was highlighted. A mammography-based surveillance programme for women at elevated risk of developing breast cancer would mean that, in contrast to no surveillance, a woman will be assessed at a younger age and undergo more mammograms throughout the course of her life. The added risk for young women who have an inherited cancer predisposition is unknown, and there is some concern whether this genetic factor may increase sensitivity to irradiation.[49]

Equity of access[121]

Decisions about healthcare distribution should consider equity of access, that is, equal access for those with equal needs. Currently women known to be at elevated risk of developing breast cancer are managed by ad hoc surveillance. In the absence of a structured programme, there may be inconsistencies in the availability and type of surveillance offered, resulting in inequitable care. A national surveillance programme operating and audited against quality key performance indicators (KPIs) that clearly identify the type and frequency of surveillance per risk group would rectify any existing equity issues that may exist in this regard.

Resource allocation[121]

The healthcare budget is finite; establishment of a breast cancer surveillance service could require reallocation of resources potentially impacting the existing healthcare system by diverting resources from other effective treatments for the same condition or from the overall healthcare fund. An organised surveillance programme could also lead to disinvestment from less effective use of resources, by, for example, curtailing existing ad hoc surveillance in certain cohorts for whom potential benefit appears to be limited. Decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity cost (the value of the next best alternative forgone) of new investments are considered. This may prove difficult as there may be many competing claims requiring prioritisation of care. Ethical issues that may inform such decisions include issues of justice and equity with respect to a fair distribution of benefits and burdens.

Other general ethical issues

The screening test should be meaningful and highly predictive[121]

The fundamental aim is to ensure that women are not exposed to surveillance unless it is proven to be safe and effective, to ensure that any harm or stress is minimised and potential benefits maximised. As noted, surveillance is a secondary preventive measure to detect breast cancer at the earliest possible stage with the aim to decrease mortality from the disease. Chapter 4 compares the diagnostic accuracy and clinical effectiveness of digital mammography and MRI for breast cancer surveillance of women at elevated risk. Although there is currently no data to support a reduction in breast cancer mortality with surveillance, there is evidence of a reduction in mortality in those at average risk through earlier detection and treatment. As highlighted in Chapter 2, five-year survival probability is strongly linked to stage at diagnosis: those diagnosed with stage I disease have 98.9% probability of survival to five years compared to 27.7% at stage IV.

The condition is serious, relevant, validated and regularly evaluated in the public health context[121]

In Ireland, breast cancer is the most common invasive cancer diagnosed in women; it is the second most common cause of cancer death (after lung cancer). As outlined in Chapter 2, a risk classification system has been adopted that classifies women as being at average, moderate or high risk based on their 10-year risk of developing breast cancer between age 40 and 50 years, or their lifetime risk. Those at moderate risk have a predicted 3% to 8% risk of developing breast cancer between age 40 and 50, and a lifetime risk of 17% up to 30%. For those at high risk, the predicted figures are >8% and ≥30%, respectively. This emphasises that breast cancer is a serious condition with consideration of surveillance being particularly relevant for those women known to be at elevated risk.

Follow-up actions (healthcare interventions) are available, the appropriate environment for prior and post testing information and counselling etc. are in place[121]

Systems for provision of information, counselling and subsequent healthcare have been established for other cancer screening programmes in Ireland. If a new surveillance programme is to have a positive impact on population health, similar systems should be developed following relevant national and European frameworks and guidelines.[106;144;148]

Pilot programmes undertaken prior to general introduction[121]

The EU commission recommends that implementation decisions should be based on experience from clinical trials and pilot programmes. Surveillance of women at elevated risk will not introduce any new techniques or technologies requiring pilot studies as both digital mammography and breast MRI are routinely used in clinical practice. The establishment of an organised surveillance programme would, however, necessitate detailed service planning to ensure that it could meet the requisite internationally accepted quality assurance standards.

Economic considerations of screening / surveillance programme[121]

The economic considerations required to extend surveillance to women at elevated risk were assessed in Chapter 5. These indicate that for all risk subgroups, MRI offers the most effective approach to surveillance in terms of increased quality-adjusted life years (QALYs) per person and reductions in breast cancer mortality, but at an increased cost. With the exception of surveillance of women with an identified genetic mutation, however, none of the surveillance options evaluated were cost-effective compared to a policy of no surveillance.

Reliability and quality assurance[121]

Any formal surveillance programme should ensure rigorous quality assurance requirements are adhered to. Currently the national guidelines for quality assurance in mammography screening,[106] quality assurance in breast cancer screening and diagnosis (EU)[144] and the NCSS Framework are in place.[148] For a national surveillance programme for breast cancer to have an impact in terms of population health, it is necessary that the NCCP introduces similar quality assurance standards to those used in its other screening programmes and regularly audits against key performance indicators (KPIs). Current national guidelines for quality assurance in mammography detail the quality assurance requirements in client care, radiography, radiology, pathology, surgery, physics, epidemiology and nursing.[106] Similar guidelines should be developed for quality assurance of MRI if this is part of the surveillance programme.

Transparency[121]

Adherence to relevant guidelines including the national and European quality assurance guidelines and the NCSS Framework should ensure a transparent and fair system.[106;144;148]

Confidentiality, the duty to disclose and warn others[121]

As noted, the remit of this HTA is limited to a cohort of women already identified as being at elevated risk of breast cancer.[148] Therefore, ethical issues associated with the identification process are beyond the scope of this work. However, the NCSS framework reports a number of important ethical issues which warrant discussion. When an individual is identified as being at elevated risk of breast cancer, it may have similar implications for family members. Most patients readily disclose this information to their family, however, a patient may refuse to do so. In this case, disclosure of patient information without their consent may be justifiable in exceptional circumstances when it is necessary to protect the patient or others from serious risk of death or serious harm.[148;149] However, the consent of the patient for disclosure should always be sought if possible.[149] Although this issue is more likely to arise when an individual is first identified as being at elevated risk, it may re-arise during a surveillance programme if a physician becomes aware that relevant family members have not been informed. The framework report also discusses confidentiality and rights of the patient with respect to the issue of obtaining insurance once deemed at high risk of developing cancer. It references the Disability Act (2005) which effectively makes it an offence for employers or insurers to obtain a person's genetic test results.[150] However, the report notes that they are still entitled to ask a person about existing medical conditions.[148] Finally, communication of test results should respect the dignity, privacy and confidentiality of the individual, and counselling should be offered to enable the individual to understand the consequences of the test result for them and other family members.

Control over samples and data[121]

The national guidelines for quality assurance[106] adhere to the Council of Europe's recommendations on screening as a tool of preventive medicine which requires that confidentiality of test results must respect the dignity, privacy and confidentiality of the individual. This means that the results of tests should be collected, stored and handled using methods that ensure confidentiality is maintained; data should not be communicated to third parties unless consent has been given. While the issue of consent may not apply with clinical audit data, case information should be anonymised to safeguard confidentiality.

Management and communication of uncertainty[121]

The Council of Europe's recommendations on screening as a tool of preventive medicine provide guidance on communication and ethical considerations.[146] For example, it discusses effective communication (comprehensive, tailored for varying

groups) using good quality information. In this case, it is not currently clear if surveillance of female carriers of the *BRAC1* or *BRAC2* gene mutations translates to any decrease in mortality. Any uncertainty of outcomes and the associated risks or benefits of surveillance in these groups as well as the available alternatives to surveillance should be communicated to allow for informed consent.

6.3 Key messages

- The main ethical issues associated with provision of a formal surveillance programme for women aged less than 50 years at elevated risk of breast cancer include informed consent particularly on the benefits versus risks of surveillance, equity of access and reallocation of resources.
- Those participating in surveillance should receive sufficient information to enable them to understand the benefits and risks associated with surveillance and the available alternatives.
- Reallocation of resources could affect the existing healthcare system as they may divert resources from other effective treatments for the same condition or from the overall healthcare fund.
- Ad hoc surveillance is currently offered to a variable extent at a local and regional level. In the absence of a structured programme, there may be inconsistencies in the availability and type of surveillance offered, resulting in inequitable care.
- The establishment of an organised surveillance programme would necessitate detailed service planning to ensure that it could meet the requisite internationally accepted quality standards. This includes the development of quality key performance indicators (KPIs) to measure performance against targets or expectations. An organised surveillance programme should improve equity of access.
- Ethical issues associated with the identification process are beyond the scope of this assessment. However, the NCSS framework report highlights a number of important ethical issues that may also arise in the delivery of a surveillance programme including the right to know and not know, and the duty to disclose and warn others.

7 Discussion

The aim of this HTA was to review the clinical and cost-effectiveness of surveillance of women less than 50 years of age at elevated risk of breast cancer due to a genetic or familial risk using either digital mammography, MRI or a combination thereof. This chapter includes a discussion of a number of issues that are relevant to the interpretation of the HTA findings. In particular, limitations of the HTA are highlighted and their likely impact on the study findings discussed.

7.1 Study population and surveillance programmes

The target population for the present study was women aged less than 50 years at elevated risk of developing breast cancer. The definition of elevated risk was adopted from the 2006 NICE guidelines[7] and is consistent with definitions used elsewhere. In any HTA, it is critical to be able to accurately characterise the target population. The number of women at elevated risk is not well known, nor is there a uniform prevalence across countries. The present study was concerned with the identified population at elevated risk, as distinct from the total population at elevated risk. The known population has been approximated to 4,487 using a variety of data sources as there is no central registry concerning the target population. In determining the total and known populations, it was apparent that there is a substantial unidentified population at elevated risk. As the cost-utility analysis is based on a cohort of 1,000 women, the results are unaffected by the true population size. The five-year budget impact analysis, on the other hand, is directly related to the population size. Should the introduction of a standardised surveillance programme be associated with increased identification of women at elevated risk, then an increased target population will lead to an increased budget impact. However, due to existing capacity constraints for family risk clinics and genetic testing, it is unlikely that there will be a substantial increase in the identified elevated risk population in the short to medium term.

Knowing the risk of developing cancer was crucial for evaluating the cost-effectiveness. Although risk levels are defined by cumulative or short-term risk, different population sub-groups within the same risk level may have quite different risk profiles over time. For example, the *TP53* cohort has a disproportionate risk before the age of 30 compared to other risk groups. Risk is not homogeneous within a risk sub-group as a variety of factors contribute to the estimate of risk including identified genetic mutations and family history. The average risk within any risk subgroup is often derived from a few relatively small studies and is not known with a great deal of precision. A sensitivity analysis undertaken in Section 5.5.6 showed that increasing risk is associated with improved cost-effectiveness, and thus a surveillance

strategy may be cost-effective for some in a risk subgroup and not for others. In the case where a woman is at the upper range of risk, it may be appropriate to offer the surveillance strategy for the next risk level on the grounds that it may provide more suitable frequency and start-age for surveillance. Additional clinical and individual factors would influence such a decision. There is also an issue of what surveillance to offer women with a suspected high penetrance genetic mutation but who have not, as yet, been tested. It may be pragmatic, as per the draft UK guidelines, to treat those with a greater than 30% probability of being *BRCA1* or *TP53* carriers as though they have that mutation and offer the corresponding surveillance until such time as genetic testing has been completed.[66] It should also be borne in mind that surveillance is optional, and some women may decide not to avail of surveillance. This was incorporated into the budget impact analysis in the form of an expected uptake rate.

There are a variety of ways in which breast cancer aetiology in women at elevated risk may differ from that in the average risk population. It is possible, for example, that tumours may be more aggressive and therefore disease progression may be faster than observed in a population at average risk. Women at elevated risk may tend to have denser breast tissue which can have implications for both diagnostic test accuracy and tumour development. Using assumptions derived from an average risk population may lead to biased estimates of the effects of a surveillance programme. In as far as was possible, the estimates of diagnostic test accuracy used in this study were based on assessments in the target population. Disease progression is more difficult to gauge, but we have used the same assumptions about time to symptomatic detection as used in a UK study that informed the 2006 NICE recommendations.[120]

Many countries currently offer surveillance for women at elevated risk of developing breast cancer (Chapter 3, Table 3.1). In published cost-effectiveness assessments, the type of imaging in use, the frequency of screens and the start age vary (Chapter 5, Table 5.1) with most assessments investigating cost-effectiveness of mammography alone or a combination of mammography and MRI. In national guidelines, the use of MRI appears to be restricted to an adjunct, to address the limitations of mammography, primarily the low test sensitivity. The evidence in favour of mammography is mainly derived from older, average risk populations. To date, there has been only limited discussion of using MRI as an alternative to digital mammography, even though its sensitivity is acknowledged to be better in younger pre-menopausal women for whom breast tissue density is higher.

Despite its widespread use, the benefit of surveillance is difficult to quantify. Surveillance generally entails increased cancer detection, particularly of DCIS. Earlier detection of invasive cancers should, in theory, lead to improved outcomes that

should be realised as reduced mortality and less debilitating treatment. Given the non-invasive nature of DCIS, increased DCIS detection does not necessarily contribute to a significant reduction in mortality. However, the majority of detected cancers are invasive. Surveillance programmes are typically implemented in the context of pre-existing arrangements, albeit non-standardised, as is the case in Ireland. As such, the major benefits of a programme are standardised care and potential efficiency gains, while health gains may be small and difficult to detect.

It is evident that many women in Ireland identified as being at an elevated risk of developing breast cancer are already receiving some form of surveillance. Through family risk clinics, relatives of women with breast cancer are assessed for risk and are then offered surveillance or reassessment depending on their level of risk. The surveillance offered is not standardised although it may depend on context over and above that encompassed by the risk level. From the CEA, it was seen that in some risk subgroups, the current ad hoc surveillance is relatively effective, but in all cases there were less costly and more effective alternatives available. For women at moderate risk, it was determined that current ad hoc surveillance is less effective than a strategy of no surveillance. Although not part of the remit of this HTA, it was identified that some women at average risk of breast cancer are currently receiving surveillance mammography. These may have been referred to a family risk clinic on the basis of an apparent elevated risk, but were subsequently reclassified following formal assessment. With the exception of the other high penetrance genetic mutations subgroup, for all subgroups the estimated ad hoc surveillance was dominated by other surveillance strategies. It must be noted, however, that what comprises current ad hoc surveillance is not clear. The assumptions for this HTA were based on a small sample that may not represent typical practice across the whole country.

7.2 Assessment model

The model used in the present HTA was a Markov model adapted from a model developed in the UK. In each simulation, a woman was modelled from age 20 to 83 in six-monthly cycles. At the end of each cycle, the woman in the model was in one of 10 discrete states. In as far as possible, the health states were chosen so as to enable accurate modelling of surveillance. By having multiple states that effectively recorded the length of time a women with invasive cancer goes undetected, it was possible to incorporate the potential benefits of early detection.

Although the preferred modelling approach, a natural history model was not used, primarily because of the difficulties in acquiring the large amount of data that would be required to define the parameters in the model. Information on disease progression and sojourn time is limited, particularly for women under 50 years of age

at elevated risk. In the absence of such data, it was pragmatic to develop a model that maximised the use of local data and data relevant to the target population. As the model does not estimate disease progression for individuals, the stage at diagnosis is sampled from an estimated distribution based on the number of years since disease onset.

The CEA model used a cohort of 1,000 women to estimate summary information such as quality-adjusted life years (QALYs) per person and cost per person for each of the risk subgroups. For a number of the subgroups, the cohort is larger than the known population. The purpose of using this cohort size is that it was sufficiently large to estimate the potential quality of life and mortality associated with different strategies without posing a significant computational burden.

The cost-utility analysis follows a cohort of women from age 20. In reality, many of the women at elevated risk are not identified until they are in their later 20s or in their 30s. As reflected in the budget impact assessment, not all eligible women will avail of surveillance and some may miss surveillance rounds for a variety of reasons, such as pregnancy. The cost-utility analysis attempts to compare each surveillance strategy on an equal footing and, by including women from the age of 20, it incorporates the possibility of modelling surveillance strategies that start from age 20.

As mentioned in the previous section, risk is assumed to be homogeneous within a risk subgroup – that is, for a given age, all women in the risk subgroup have the same risk of developing breast cancer. While this is a convenience from a modelling perspective, it does mean that the results are based on the average risk within a risk subgroup. Hence although a strategy may be, on average, not cost-effective, it may be for some in a particular risk group, and vice versa. This is an unavoidable difficulty in modelling interventions for target populations with heterogeneous risk profiles. A scenario analysis of varying risk showed that cost-effectiveness improves with increasing risk. However, surveillance based on exact risk levels supposes that precise estimate of individual risk is feasible, which may not be the case in practice.

The model includes both invasive breast cancer and ductal carcinoma in situ (DCIS). Some DCIS will develop into invasive cancers while others could go undetected in the absence of surveillance and not cause morbidity or mortality. A detected DCIS will always be removed although there is a possibility that it will never develop further. As such, a surveillance or screening programme will result in the detection and treatment of cancers that do not contribute to mortality. The cost of no surveillance may therefore be lower than for a surveillance programme due in part to fewer cancers treated.

In the model it was assumed that the rate of disease progression is such that even in the absence of any surveillance programme, cancers will be symptom-detected after two years. When women are symptom-detected, the model assumed a greater probability of later stage at diagnosis and consequently lower survival rates. The target population are likely to be well informed of their elevated risk and are likely to be quite diligent in breast self-examination and regular check-ups, so it is possible that early detection is more likely. However, this must be offset by the possibility of a faster disease progression than might be observed in an average risk population.

The budget impact assessment estimated the costs and certain resource implications over five years for each surveillance strategy. The BIA was based on the size of the known population, and hence the accuracy is a function of the accuracy of the population estimates. In many cases, the known cohort is relatively small and thus the budget impact is subject to a great deal of variability.

Two comparators were used in the study: no surveillance and the existing ad hoc system of surveillance. Both were necessary as the latter represents the current standard of care, while the former provides a universal reference standard. The frequency and intensity of ad hoc surveillance is not known with much accuracy. It is likely that, at the time of this HTA, the 2006 guidelines developed by NICE regarding MRI surveillance are being applied to women with identified high penetrance genetic mutations. It is possible that digital mammography surveillance for women with identified high penetrance genetic mutations starts at 35 or even 30, compared to the 2006 NICE recommendation of starting at 40. However, for high familial risk in the absence of an identified genetic mutation or for moderate risk, the surveillance patterns were estimated from family risk clinic data. It is likely that surveillance patterns vary greatly across the country and the data used in the study may not be nationally representative. For some of the risk subgroups, it would appear that strategies may be cost-effective compared to ad hoc surveillance, but not when compared to no surveillance. Indeed, in the case of the moderate risk group it appears that ad hoc surveillance is less effective than no surveillance. This interpretation should be viewed with some caution. It must again be stressed that the cancer risk is heterogeneous within any risk subgroup. It is possible that those currently receiving surveillance that appears to be inappropriate for their risk subgroup, may have a higher risk than is typical for their risk subgroup. The family risk clinic data did not provide a level of detail that identified estimates of risk at an individual level, only at the level of the risk subgroup.

The model incorporates an estimate of increased risk due to radiation exposure from digital mammography based on the likely radiation dose. The additional risk generated by radiation exposure results in cases of breast cancer that would not have occurred in the absence of a surveillance programme. The increase in risk is

cumulative, such that a higher frequency of mammograms will lead to a higher risk increase than a lower frequency of mammograms. The impact of the increased risk is therefore a function of both baseline risk and surveillance frequency and so varies for each risk subgroup and surveillance strategy. There is therefore a trade-off between timely detection possible with higher frequency mammography surveillance and more induced cancers. There is evidence to suggest that early radiation exposure in *BRCA* mutation carriers through mammography may increase breast cancer risk over and above what has been observed in other cohorts.[112] As MRI is not associated with radiation exposure, it does not induce cases of breast cancer.

7.3 Data

The accuracy of model outputs is a function of the model inputs and how they are combined. A large number of parameters were derived from a variety of sources mixing both local and international data. In many cases, the data were not specific to the elevated risk groups that defined the target population. A univariate sensitivity analysis was used to establish which parameters contributed most to uncertainty in the model results.

The diagnostic test accuracy is clearly a major factor in assessing a screening or surveillance programme. Two imaging techniques were being considered in this study: digital mammography and MRI. It was important to gather data on test accuracy relevant to the target population. However, few studies have assessed test accuracy in women at elevated risk of developing breast cancer, and only a small subset considered women less than 50 years of age. While it is assumed that the test accuracy of MRI is largely unaffected by breast density, that is not the case for mammography. The evidence around the test accuracy of digital mammography in the target population is very limited and not entirely consistent. A conservative estimate was used in the model for the diagnostic test accuracy of digital mammography. The accuracy of film mammography was used as a proxy, as some studies indicate that this may be an appropriate assumption in women less than 50 years old. A number of the studies in the systematic review and meta-analysis did include digital mammography or a mix of digital and film mammography. From these studies it was apparent that the estimated diagnostic test accuracy of digital mammography was similar to that of film mammography in the target population.[63;70] A scenario analysis estimated the impact of increasing the test sensitivity of digital mammography from the 38% used in the main model to 50%. While this reduced the ICER of digital mammography surveillance strategies relative to a 'no surveillance' option, it did not result in any of the digital mammography surveillance strategies moving onto the cost-effectiveness frontier. The evidence of diagnostic accuracy used in the study is also based on annual screening, which is

unlikely to be generalisable to other surveillance frequencies, such as biannually. For biennial strategies, we adjusted the test sensitivity for both digital mammography and MRI based on observed difference inferred from US data. These data suggest a modest increase in test sensitivity of approximately 5% when the test frequency is every 18 months and over.

As discussed previously, outcomes stemmed from stage at diagnosis. Data from the National Cancer Registry Ireland were used to estimate typical stage at diagnosis for women under 50 in the general population who are screen-detected and symptom-detected. To what extent this applies to women at elevated risk is debateable, although women at elevated risk are likely to contribute disproportionally to breast cancer in women less than 50 years. The data provide sampling weights that are used to determine stage at diagnosis, rather than providing an average which would not, in any case, be appropriate for a discrete distribution. Screen-detected cases will on average have a lower stage at diagnosis than symptom-detected cases. However, the use of sampling means that a screen-detected case could be diagnosed at stage IV while a symptom-detected case could be diagnosed at stage I. This gives rise to the occasional inconsistency where a screen-detected case has a poorer outcome than an equivalent symptom-detected case. The model for each strategy was run with 5,000 simulations and checked for stability of outcome estimates. The use of a large number of simulations as well as use of differences of medians rather median of differences guards against the risk of inconsistencies impacting on decision making.

Treatment was estimated as a function of stage at diagnosis. The proportion of patients receiving each form of treatment was obtained from a number of sources, including the National Cancer Registry Ireland, local hospital databases and the advice of the EAG. The data on treatment did not impact on the calculation of health outcomes, but did directly contribute the estimate of costs. A scenario analysis showed that the calculated ICERs compared to 'no surveillance' were largely unaffected by using different assumptions about proportions receiving each form of treatment. However, the situation highlighted the difference between data apparently representative of routine practice and opinion on what should be standard practice.

Survival rates were obtained from the National Cancer Registry and are based on the total population of women aged less than 50 years diagnosed with breast cancer. The survival data used in the study was specific to five-year survival. In the model it was assumed that any women surviving to five years would have normal life expectancy thereafter. This is a simplification as it can be anticipated that, for example, 10-year survival will be lower than for the general population. The survival data are based on 10-year age bands by stage at diagnosis. In some cases, survival

improves substantially from one age group to the next. This has the potential to cause inconsistencies in the model as survival is computed based on age at diagnosis. For example, a stage II cancer diagnosed at age 29 has a probability of mortality of 0.162, compared to 0.086 for the same cancer diagnosed at age 30. In rare cases, deferred diagnosis may paradoxically lead to an improved outcome, although on average deferred diagnosis should lead to a later stage at diagnosis. Again, the use of many model simulations protects against results being influenced by inconsistencies that may arise.

As a cost-utility analysis was used, health-related quality of life (HRQoL) data were used in the model. HRQoL was assumed to diminish with age. Values were also used specific to treatment by stage at diagnosis, false positives, and terminal cancer. The applicability of HRQoL data is always open to debate, and different studies may obtain quite different estimates of HRQoL for apparently the same condition and population. The values used in this study follow a clear and consistent gradient such that the disutility associated with false positives is smallest, followed by an increasing disutility associated with treatment for later stages. Finally, the quality of life is lowest for those with terminal cancer.

The model included costs for the surveillance imaging, further testing of positive screens, and cancer treatment. There were difficulties in determining costs in all cases. Estimates were obtained from a variety of sources, often with differences that could be reconciled. For the cost of MRI, a micro-costing exercise was undertaken with UK data used to determine the likely range of costs. The cost of MRI in Ireland was estimated to be slightly higher than in the UK. Given the sensitivity of the model to the choice of screening cost, it was important to obtain accurate estimates. In the univariate sensitivity analysis, varying the cost of MRI by ±12% resulted in a ±4.5% change in total cost. An equivalent variation in digital mammography cost resulted in a ±3.3% change in total cost.

For surgical costs, figures were originally obtained from a patient-level-costings exercise by a public acute hospital. However, the values were inconsistent with the DRG costings for day case and inpatient episodes for the relevant procedures. Given that casemix represents the funding mechanism in public acute hospitals in Ireland, it was deemed that this approach would generate costs in line with how much hospitals currently receive. The average cost of treatment ranged from €9,352 for a woman with DCIS to €24,212 for a woman with stage III cancer. The largest contributor to treatment cost was chemotherapy, and uncertainty in the cost of chemotherapy was a major contributor to uncertainty in the total cost of surveillance. The contribution of treatment costs to total cost depends on the strategy being modelled, although it is typically 60% of the total cost. Treatment contributes least to total cost in a high frequency, early start MRI surveillance strategy, where the

imaging costs will be high. In a low frequency, late start digital mammography strategy, for example, treatment will contribute a greater proportion of total cost.

The uptake rate of surveillance was included in the budget impact assessment. The same estimates were used for all risk subgroups and based on digital mammography surveillance strategies. It is unlikely that uptake rates would be greatly affected by the choice between MRI and digital mammography, although rates may be affected by risk level. Women at higher risk may be more likely to avail of surveillance on the grounds that they will have a greater awareness of their risk and the benefits of early detection. Uptake rates may be impacted by surveillance frequency, as high frequency surveillance may entail greater inconvenience in travel to and from surveillance clinics. It is possible that there is a correlation between uptake rates and the rate of prophylactic surgery, in so far as the factor impacting on the decision to avail of surveillance may also influence the decision to avail of prophylactic surgery. There was little evidence available on either uptake rates or prophylactic surgery, and no data on the possible correlations that may exist between the two options. The study used international data relevant to the target population which should be representative, although regional variations may mean that an Irish population may behave differently.

7.4 Key messages

- Although the definitions of the risk subgroups are clear, the population is poorly identified and understanding of disease pathology and progression in these cohorts is not fully defined.
- The benefits of surveillance are based on assumptions of early detection leading to improved outcomes. Disease progression and pathology in women with high penetrance genetic mutations may be different from older women at average risk, which may impact on the benefits of surveillance.
- Where possible, the model used in this study incorporated data specific to the target population. However, for some parameters the underlying data relate to an average risk population, which will potentially have affected the results.

8 Conclusions

Health technology assessment supports evidence-based decision making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The purpose of this HTA was to examine the potential provision of a national surveillance programme for women aged less than 50 years at elevated risk of breast cancer due to a genetic predisposition or a strong family history. Evidence of the safety and effectiveness of digital mammography and magnetic resonance imaging (MRI) were assessed as well as the cost-effectiveness and budget impact of various surveillance options compared to the current practice of no organised surveillance, and to no surveillance.

8.1 Burden of disease

Breast cancer is the most common invasive cancer in women in Ireland, accounting for 32% of all cases of invasive cancer and 16% of female cancer-related deaths. Twenty-five percent of diagnoses are in women aged less than 50 years, with 10% of deaths, an average of 88 deaths per annum between 2005 and 2010, occurring in this age group. Prognosis is strongly linked to stage of diagnosis, with five-year survival probability of 98.9% for those diagnosed at stage I compared to 27.7% when diagnosed at stage IV.

Women are classified as being at average, moderate or high risk of breast cancer if their 10-year risk of breast cancer between ages 40-50 years is less than 3%, between 3% and 8% and greater than 8%, respectively. Women at high risk of breast cancer contribute disproportionately to the incidence of early breast cancer. Although comprising less than 3% of the population, women at high risk of developing breast cancer are estimated to contribute 13% to incidence in women aged less than 50 years. Although the definitions of the risk subgroups are clear, the population is poorly identified and understanding of disease pathology and progression in these cohorts is ill-defined.

8.2 Clinical effectiveness and safety of technologies

Two imaging modalities were compared in this study: digital mammography and MRI. The estimated sensitivity and specificity of digital mammography for the target population are 0.38 and 0.97, respectively. These estimates are based primarily on film mammography data due to the lack of studies comparing digital mammography and MRI in women at elevated risk of breast cancer. Exposure to radiation through a mammography-based surveillance programme from a young age may increase the

risk of developing breast cancer. The estimated sensitivity and specificity of MRI for the target population are 0.80 and 0.92, respectively; there is no radiation exposure associated with MRI.

The overall effectiveness of a surveillance programme for women at elevated risk of breast cancer depends on the combination of age range, imaging modality and surveillance interval used. International practice varies, however, current use of MRI is often as an adjunct to mammography. While there is evidence of a mortality reduction in average risk populations through earlier detection and treatment, there is a lack of data specific to women under 50 at an elevated risk of breast cancer. Disease progression and pathology in women under 50 at elevated risk may be different from older women at average risk, which may impact on the benefits of surveillance. Surveillance has non-mortality effects that are both positive (e.g., early detection leading to improved survival) and negative (e.g., radiation-induced carcinoma, overdiagnosis and unnecessary biopsies). The ratio of benefits to harms depends on the target population.

8.3 Cost-effectiveness, budget impact and resource requirements

For women aged less than 50 years with identified high penetrance genetic mutations, surveillance offers a significant opportunity to reduce mortality. From a cost-effectiveness perspective, annual MRI from age 25 or 30 is the recommended strategy for those with *BRCA1, BRCA2* and other high penetrance genetic mutations other than *TP53* (i.e. both more effective and less costly than the current practice of offering annual MRI from age 30 plus digital mammography [DMX] in combination from age 30 or 35). The addition of annual digital mammography from age 40 would be in accordance with current international practice. For the subgroup with *TP53* mutations, annual MRI surveillance from age 20 is the recommended strategy, with no digital mammography prior to age 50.

For women at high familial risk with no identified genetic mutations, surveillance before the age of 40 is not recommended on the basis of cost and clinical effectiveness. While surveillance is not cost-effective from ages 40 to 49 compared to no surveillance, providing annual MRI-based surveillance is preferable to existing ad hoc surveillance and offers the potential of a minor mortality reduction. Given the questionable feasibility of such an increased demand for MRI imaging, annual digital mammography from age 40 to 49, in accordance with current international practice, would be less costly and more effective than existing ad hoc surveillance.

For women at moderate risk, surveillance before the age of 40 is not recommended on the basis of cost or clinical effectiveness. Similar to women with high familial risk,

surveillance is not cost-effective from ages 40 to 49 compared to no surveillance. However, providing annual MRI-based surveillance is less costly than existing ad hoc surveillance and offers the potential of a minor mortality reduction. If it is considered impractical to offer MRI-based surveillance to such a large cohort, but offering some form of standardised surveillance is considered desirable, then annual digital mammography from age 40 to 49 would be less costly and more effective than existing ad hoc surveillance.

The known population of women aged less than 50 who are carriers of high penetrance genetic mutations is relatively small. As a consequence, the incremental budget impact of different surveillance strategies for this cohort tends to be small. However, the small size of the cohort means that potential mortality reductions are small in absolute terms. Compared to current ad hoc surveillance, the recommended surveillance strategies will result in a modest reduction in budget impact, a reduction in digital mammography requirements, and no substantive change in the number of MRIs and MR-guided biopsies over the course of five years.

8.4 Ethical considerations

The main ethical issues associated with provision of a formal surveillance programme for women aged less than 50 years at elevated risk of breast cancer include informed consent particularly on the benefits versus risks of surveillance, equity of access and reallocation of resources. Ad hoc surveillance is currently offered to a variable extent at a local and regional level. In the absence of a structured programme, there may be inconsistencies in the availability and type of surveillance offered, resulting in inequitable care.

Those invited for surveillance should receive sufficient information to enable them to fully understand the benefits and risks of surveillance and to understand the alternatives. The establishment of an organised surveillance programme would necessitate detailed service planning to ensure that it could meet the requisite internationally accepted quality standards. This includes the development of quality key performance indicators (KPIs) to measure performance against targets or expectations. An organised surveillance programme should improve equity of access.

8.5 Advice to the National Cancer Control Programme

As economic models incorporate a number of assumptions and are dependent on the quality of data available, the results are subject to a degree of uncertainty. Bearing in mind the estimates and assumptions that were used in this analysis and arising from the findings above, the Authority's advice to the National Cancer Control Programme is as follows:

- Surveillance is cost-effective compared to no surveillance for women aged less than 50 years with an identified high penetrance genetic mutation. For women aged less than 50 years with either high familial risk and no identified genetic mutation or those at moderate risk, surveillance is not cost-effective by traditional standards when compared to no surveillance.
- For women aged less than 50 years with identified high penetrance genetic mutations other than *TP53*, annual MRI from age 30 to 49 is recommended. The addition of annual digital mammography from age 40 to 49 could be offered to maintain accordance with current international practice.
- For the subgroup with a *TP53* mutation, annual MRI surveillance from age 20 to 49 is recommended.
- For women at high familial risk with no identified genetic mutations, annual digital mammography from ages 40 to 49 is preferable to existing ad hoc surveillance.
- For women at moderate risk, annual digital mammography from ages 40 to 49 is preferable to existing ad hoc surveillance.
- An organised surveillance programme will improve equity of access; it should have quality key performance indicators (KPIs) to measure performance against targets or expectations.

Glossary of terms

Adverse event	Any noxious, pathological or unintended change in anatomical, physical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of a clinical study whether or not considered treatment related. It includes exacerbation of pre-existing conditions or events, intercurrent illnesses, accidents, drug interaction or the significant worsening of disease.
Asymptomatic	Without symptoms. For example, an asymptomatic infection is an infection with no symptoms.
Autonomy	The patient's right of self-determination concerning medical care. It may be used in various senses including freedom of action, effective deliberation and authenticity. It supports such moral and legal principles as respect for persons and informed consent. Making decisions for oneself, in light of a personal system of values and beliefs.
Bayesian analysis	A statistical approach that can be used in single studies or meta-analysis which explicitly incorporates a prior probability distribution based on subjective opinion and objective evidence, such as the results of previous research.
Bias	In general, any factor that distorts the true nature of an event or observation. In clinical investigations, a bias is any systematic factor other than the intervention of interest that affects the magnitude of (i.e. tends to increase or decrease) an observed difference in the outcomes of a treatment group and a control group.
Budget impact analysis	The financial impact of the introduction of a technology or service on the capital and operating budgets of a government or agency.
Capital costs	The non-recurring cost of investment in items that remains useful beyond the period when costs are incurred.
Casemix	The mix of patients treated by a hospital in terms of treatment complexity. Reimbursement for the cost of patient care in the Irish public hospital system is based on casemix.
Clinical outcome	An outcome of major clinical importance that is defined on the basis of the disease being studied (e.g. fracture in osteoporosis, peptic ulcer healing and relapse rates).
Clinical significance	A conclusion that an intervention has an effect that is of practical meaning to patients and healthcare providers.

Cohort study	An observational study in which outcomes in a group of patients that received an intervention are compared with outcomes in a similar group, i.e. the cohort, either contemporary or historical, of patients that did not receive the intervention.
Comparator	The technology to which an intervention is compared.
Complication	A secondary disease or condition that develops in the course of a primary disease or condition and arises either as a result of it or from independent causes.
Confidence interval (CI)	Depicts the range of uncertainty about an estimate of a treatment effect.
Contraindication	A clinical symptom or circumstance indicating that the use of an otherwise advisable intervention would be inappropriate.
Cost per QALY	A measure used in cost utility analysis (CUA) to assist in comparisons among programmes; expressed as monetary cost per unit of outcome.
Cost-effectiveness analysis (CEA)	A comparison of alternative interventions in which costs are measured in monetary units and outcomes are measured in non-monetary units, e.g. reduced mortality or morbidity. (See also **Cost per QALY**).
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis of alternative interventions in which costs are measured in monetary units and outcomes are measured in terms of their utility, usually to the patient, e.g. using QALYs.
DRG	The diagnosis related group (DRG) is a code that classifies a hospital episode according to three components: the major diagnosis category; surgical, medical or 'other' episode type; and severity of episode. DRGs are used as the basis for costing hospital episodes. In Ireland, the Australian refined (AR) version of DRGs is used.
Digital mammography	See **Mammography**
Discount rate	The interest rate used to discount or calculate future costs and benefits so as to arrive at their present values, e.g. 3% or 5%. This is also known as the opportunity cost of capital investment.
Discounting	The process used in cost analyses to reduce mathematically future costs and/or benefits/outcomes to their present value.
Economic evaluation	The comparative analysis of alternative courses of action, in terms of their costs and consequences.

Economic model	In healthcare, a mathematical model of the patient pathway that describes the essential choices and consequences for the interventions under study and can be used to extrapolate from intermediate outcomes to long-term outcomes of importance to patients.
Effectiveness	The benefit (e.g. to health outcomes) of using a technology for a particular problem under general or routine conditions.
Efficacy	The benefit of using a technology for a particular problem under ideal conditions, for example, in a laboratory setting or within the protocol of a carefully managed randomised controlled trial.
Efficiency	The extent to which the maximum possible benefit is achieved out of available resources.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations.
Equity	Fairness in the allocation of resources or treatments among different individuals or groups.
Ethics	A general term for what is often described as the science of morality. In philosophy, ethical behaviour is that which is good. The goal of a theory of ethics is to determine what is good, both for the individual and for society as a whole.
Evidence-based medicine	The use of current best evidence from scientific and medical research to make decisions about the care of individual patients. It involves formulating questions relevant to the care of particular patients, systematically searching the scientific and medical literature, identifying and critically appraising relevant research results, and applying the findings to patients.
Film mammography	See **Mammography**
Forest plot	A plot showing a series of lines and symbols which represent the results of a meta-analysis.
Funnel plot	A graphical display of sample size plotted against effect size that can be used to investigate publication bias.
Germline mutation	A mutation that may be passed on to offspring.
Health outcomes	The results or impact on health of any type of intervention (or lack of), e.g. a clinical procedure, health policy or programme, etc..
Health-related quality of life (HRQoL)	A multi-dimensional measure comprising the physical and mental health perceptions of a patient in terms of health status, health risks, functional status, social support, and socioeconomic status.

Health technology	Any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. This includes the pharmaceuticals, devices, procedures and organisational systems used in healthcare.
Health technology assessment (HTA)	Health technology assessment (HTA): the systematic evaluation of properties, effects, and/or impacts of healthcare technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in healthcare. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.
Heterogeneity	In meta-analysis, heterogeneity refers to variability or differences in the estimates of effects among studies. Statistical tests of heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance.
Hierarchy of evidence	Studies are often grouped into a hierarchy according to their validity or the degree to which they are not susceptible to bias. The hierarchy indicates which studies should be given most weight in an evaluation.
HTA	Health technology assessment.
Iatrogenic	An adverse condition in a patient resulting from treatment by a physician or surgeon.
Incidence	The rate of occurrence of new cases of a disease or condition in a population at risk during a given period of time, usually one year.
Incremental cost	The additional costs that one intervention imposes over another.
Incremental cost-effectiveness ratio (ICER)	The ratio of incremental costs to incremental benefits (difference in effect of patient outcome) obtained when comparing two technologies, e.g. additional cost per QALY.
Indication	A clinical symptom, risk factor, or circumstance for which the use of a particular intervention would be appropriate as determined or specified.
Informed consent	The legal and ethical requirement that no significant medical procedure can be performed until the competent patient has been informed of the nature of the procedure, risks and alternatives, as well as the prognosis if the procedure is not done. The patient must freely and voluntarily agree to have the procedure done.
Justice	The principle that states that fairness requires equals to be treated equally.

Literature review	A summary and interpretation of research findings reported in the literature. May include unstructured qualitative reviews by single authors as well as various systematic and quantitative procedures such as meta-analysis. (Also known as overview.)
Magnetic resonance imaging (MRI)	See **MRI**.
Malignant	Tending to invade normal tissue or to recur after removal; cancerous.
Mammography	A mammogram is an X-ray of the breast that is used in breast cancer detection. In digital mammography a digital detector is used instead of the image receptor found in film screen mammography. The use of digital mammography enables remote assessment and interpretation as well as manipulation of the retrieved image to improve visualisation.
Mean (arithmetic mean)	The average value, calculated by summing all the observations and dividing by the number of observations.
Median	The middle value in a ranked group of observations. This can be a better estimate of the average value if there are extreme outlying values that may skew the arithmetic mean.
MEDLINE	An electronic database produced by the United States National Library of Medicine.
Menarche	The first menstrual period of a woman.
Meta-analysis	Systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome.
Metastasis	The development of secondary malignant growths at a distance from the primary site.
Methodological quality	The extent to which the design and conduct of a study are likely to have prevented systematic errors (bias).
MRI	Magnetic resonance imaging (MRI) is a medical imaging technique used in radiology to visualise internal structures of the body. Unlike CT scans or traditional X-rays, MRI does not use ionising radiation.
Natural history	The course of a disease from onset (inception) to resolution. Many diseases have well-defined stages such as pathological onset, pre-symptomatic and clinically manifest disease.
Neoplasm	A new and abnormal growth of tissue in some part of the body, especially as a characteristic of cancer.

Oncology	The study of tumours.
Opportunity cost	The amount that could be spent on alternative healthcare strategies if the health technology in question was not used.
Outcomes	Components of patients' clinical and functional status after an intervention has been applied.
p value	In hypothesis testing, the probability that an observed difference between the intervention and control groups is due to chance alone if the null hypothesis is true.
Parenchymal enhancement	The normal enhancement of the patient's fibroglandular tissue in a contrast-enhanced MRI image. This form of enhancement can impact on the accuracy of MRI for invasive cancer detection.
Pathology	The anatomic and physiological deviations from the normal that constitute disease or characterize a particular disease.
Postoperative	Relating to, occurring in, or being the period following a surgical operation.
Preference	Preference is a generic term and a concept that refers to the desirability of a health outcome. Both utility and value are special cases of the general term/concept of preference.
Prevalence	The number of people in a population with a specific disease or condition at a given time, usually expressed as a proportion of the number of affected people to the total population.
PubMed	A service of the National Library of Medicine that includes over 14 million citations for biomedical articles back to the 1950s.
Quality of evidence	Degree to which bias has been prevented through the design and conduct of research from which evidence is derived.
Quality of life (QOL)	See **Health-related quality of life**.
Quality-adjusted life year (QALY)	A unit of healthcare outcomes that adjusts gains (or losses) in years of life subsequent to a healthcare intervention by the quality of life during those years.
Random effects model	A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.
Randomised controlled trial (RCT)	An experiment of two or more interventions in which eligible people are allocated to an intervention by randomisation. The use of randomisation then permits the valid use of a variety of statistical methods to compare outcomes of the interventions.

Relative risk (RR) (risk ratio)	The ratio of (statistical) risk in the intervention group to the risk in the control group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes an RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.
Reliability	The extent to which an observation that is repeated in the same, stable population yields the same result (i.e. test-retest reliability).
Retrospective study	A study in which investigators select groups of patients that have already been treated and analyse data from the events experienced by these patients.
Risk assessment	The qualitative or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards or from the absence of beneficial influences.
Risk factor	An aspect of a person's condition, lifestyle or environment that increases the probability of occurrence of a disease. For example, cigarette smoking is a risk factor for lung cancer.
RR	See **Relative Risk**.
SD	See **Standard deviation**.
Selection bias	Error due to systematic differences in characteristics between those who are selected for study and those who are not.
Sensitivity analysis	A means to determine the robustness of a mathematical model or analysis (such as a cost-effectiveness analysis or decision analysis) that tests a plausible range of estimates of key independent variables (e.g. costs, outcomes, probabilities of events) to determine if such variations make meaningful changes to the results of the analysis.
Standard deviation (SD)	A measure of the dispersion of a set of data from its mean.
Statistical significance	Statistical significance: a conclusion that an intervention has a true effect, based upon observed differences in outcomes between the treatment and control groups that are sufficiently large so that these differences are unlikely to have occurred due to chance, as determined by a statistical test.
Stochastic	A stochastic process is one that involves random elements so that the outcome varies each time the process is repeated.
Study validity	The degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).

Subgroup analysis	The process of analysing data from subpopulations of patients. Sub-group analyses should be planned at the outset of the study and even then their results should only be considered as exploratory.
Systematic review (systematic overview)	A form of structured literature review that addresses a question that is formulated to be answered by analysis of evidence, and involves objective means of searching the literature, applying predetermined inclusion and exclusion criteria to this literature, critically appraising the relevant literature, and extraction and synthesis of data from the evidence base to formulate findings.
Utility	In economic and decision analysis, the desirability of a specific level of health status or health outcome, usually expressed as being between zero and one (e.g. death typically has a utility value of zero and a full healthy life has a value of one).
Validity	The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors). Also, the degree to which a measure or parameter accurately reflects or assesses a concept of interest.
Variance	A measure of the variation shown by a set of observations, defined by the sum of the squares of deviations from the mean, divided by the number of degrees of freedom in the set of observations.
Willingness to pay (WTP)	The maximum amount that a person is willing to pay: (i) to achieve a particular good health state or outcome, or to increase its probability of occurrence; or (ii) to avoid particular bad health state or outcome, or to decrease its probability.

Appendix 1 – Literature search strategies

A literature search was conducted to identify studies examining the sensitivity and specificity of mammography, MRI or mammography and MRI combined in women with an elevated risk of developing breast cancer. The following databases were searched for original studies: MEDLINE, Embase and the Cochrane Central Register of Controlled Trials. A search for previous systematic reviews as well as other reviews and HTAs on this research question was conducted in MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment database. These reports were examined in order to identify any additional studies for inclusion. The initial search covered the period up to 7 November 2011; no starting time limit was specified. The search was re-run on 18 December 2012 and one additional study was identified for inclusion in the meta-analysis.

The PICO analysis used to structure the search strategy was as follows;

Population:	Women under 65 at an elevated risk of breast cancer.
Intervention:	MRI, Mammography or MRI & Mammography combined
Comparator:	MRI, Mammography or MRI & Mammography combined
Outcome:	Sensitivity and specificity of each diagnostic test

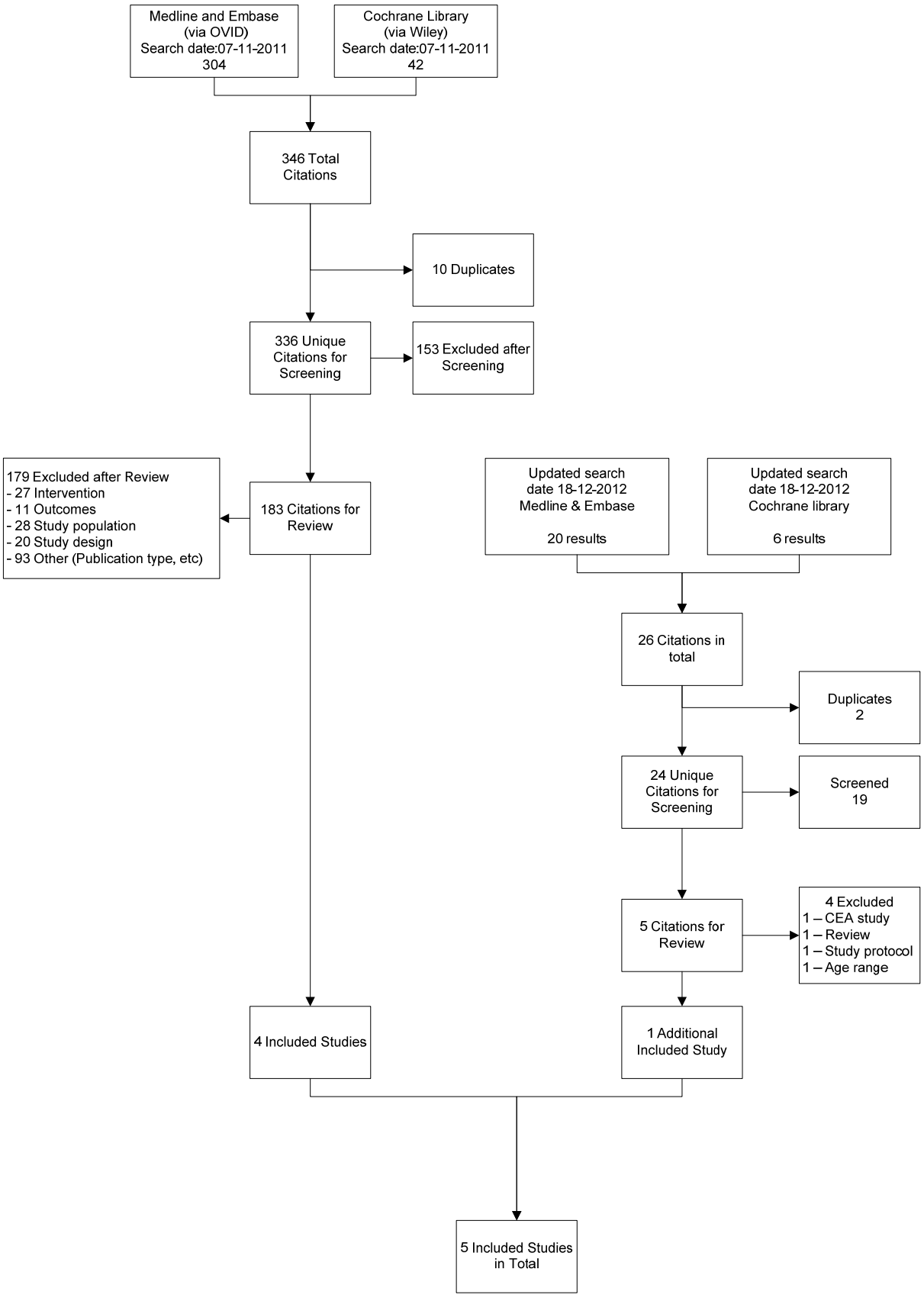
MEDLINE and Embase were searched using the OVID platform. The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and the Health Technology Assessment database were searched through the Cochrane Library. Details of the search terms used (Table App 1.1) and a flowchart of the results of the search (Figure App 1.1) are provided below. The initial set of citations was screened by one reviewer (PM) to eliminate results which were unrelated to breast cancer detection in high risk populations. All remaining citations were independently reviewed by two people (PM, CT) and any disagreements were settled through discussion (Table App 1.2). Data extraction from included studies was also performed independently by both reviewers and any differences were settled through discussion and/or re-examination of the data. Quality of included studies was assessed using the abbreviated QUADAS tool developed by the Cochrane Diagnostic Accuracy Working Group.[69] Quality assessment tables and figures were produced using Revman[68] software (Tables App 1.2-1.15). Studies comparing MRI and mammography in women at elevated risk of breast cancer that were excluded from the analysis are summarised in Table App 1.16 along with the reason for their exclusion.

Table App 1.1 Literature search terms

OVID Search Strings
breast.ti,ab.
mammary.ti,ab.
1 or 2
cancer.ti,ab.
carcinoma$1.ti,ab.
neoplasm$1.ti,ab.
tumo?r$1.ti,ab.
lesion$1.ti,ab.
metasta$.ti,ab.
or/4-9
3 and 10
diagnos$.ti,ab.
screen$.ti,ab.
surveillance.ti,ab.
detect$.ti,ab.
test$3.ti,ab.
or/12-16
mri.ti,ab.
magnetic resonance imaging.ti,ab.
mr imaging.ti,ab.
zeugmatography.ti,ab.
mammogra$.ti,ab.
ffdm.ti,ab.
or/18-23
high$ risk.ti,ab.
increased$ risk.ti,ab.
elevat$ risk.ti,ab.
brca.ti,ab.
family history.ti,ab.
first degree relative.ti,ab.
blood relative.ti,ab.
genetic.ti,ab.
inherited.ti,ab.
familial.ti,ab
hereditary.ti,ab.
or/25-35
sensitivity.ti,ab.
specificity.ti,ab.
sn.ti,ab.
sp.ti,ab.
or/37-40
11 and 17 and 24 and 36 and 41

Cochrane Library Search Strings
(breast OR mammary) AND (cancer OR carcinoma OR neoplasm* OR tumor OR metatstat* Or tumour OR lesion OR lesions)
AND
diagnos* OR screen* OR surveillance OR detect* OR test*
AND
mri OR MRI OR "magnetic resonance" OR "MR imaging" OR zeugmatography OR mammogra* OR FFDM
AND
sensitivity OR specificity OR sp OR sn
AND
risk OR brca OR BRCA OR family OR relative OR genetic OR hereditary OR familial OR inherited

Figure App 1.1 Search results flowchart



Summary of included studies

Table App 1.2 Summary of included studies

Study Name	Country	N	Imaging modality	Frequency of screening	Follow-up	Sensitivity	Specificity
Kriege 2006[46]	Netherlands	1365	FMX	Annual	1-4 years	0.36 [0.20, 0.55]	0.95 [0.94, 0.96]
			MRI			0.70 [0.51, 0.84]	0.89 [0.88, 0.90]
Kuhl 2005[63]	Germany	529	FMX	Annual	2-7 years	0.33 [0.19, 0.49]	0.97 [0.96, 0.98]
			MRI			0.91 [0.78, 0.97]	0.97 [0.96, 0.98]
Leach 2005[42]	United Kingdom	649	FMX	Annual	2-7 years	0.40 [0.24, 0.58]	0.93 [0.92, 0.95]
			MRI			0.77 [0.60, 0.90]	0.81 [0.80, 0.83]
Warner 2004[62]	Canada	236	FMX	Annual	1-3 years	0.36 [0.17, 0.59]	1.00 [0.99, 1.00]
			MRI			0.77 [0.55, 0.92]	0.95 [0.93, 0.97]
Sardanelli 2011[70]	Italy	501	FMX & DMX	Annual	1-4 years	0.45 [0.24, 0.68]	0.99 [0.98, 0.99]
			MRI			0.89 [0.65, 0.99]	0.97 [0.95, 0.98]

Characteristics of included studies

Table App 1.3 Characteristics of included studies – Kriege 2006

Kriege 2006[46]	
Clinical features and settings	Surveillance scheme for asymptomatic women with an increased risk of breast cancer due to a familial or genetic disposition, being seen at a family cancer clinic in the Netherlands
Participants	1,365 participants were premenopausal at study entry - 244 of these were tumour suppression gene mutation carriers (*BRCA1*, *BRCA2*, *PTEN* or *TP53*) - 754 were classified as high risk (cumulative lifetime risk of 30% to 49%) - 376 were moderate risk (cumulative lifetime risk of 15% to 29%)
Study design	Non-randomised prospective comparative cross-sectional cohort study
Target condition and reference standard(s)	Breast cancer Cytologic or histologic evaluation of a biopsy specimen was the reference standard for positive tests, negative tests were confirmed through follow-up.
Index and comparator tests	Annual mammography and MRI
Follow-up	Median follow-up of 2.9 years
Notes	

Table App 1.4 Assessment of methodological quality – Kriege 2006

Item	Authors' judgment	Support for judgment
Representative spectrum?	Yes	"women with a genetic risk of breast cancer were recruited for the study by six familial-cancer clinics in the Netherlands"..."Of the women who were invited to participate in the study, 90 percent agreed"...19% were mutation carriers, 55% were high risk, 26% were moderate risk
Acceptable reference standard?	Yes	"When one of the two examinations was scored as BI-RADS category 4 ("suspicious abnormality") or category 5 ("highly suggestive of malignancy"), a cytologic or histologic evaluation of a biopsy specimen was performed."
Acceptable delay between tests?	Yes	Mammography and MRI performed within a 6-weeks period
Partial verification avoided?	Yes	All positive index tests were biopsied, all negative index tests were followed up
Differential verification avoided?	No	The biopsy test was only used on those for whom a positive result was obtained using the index test
Incorporation avoided?	No	Biopsy relies on imaging test to identify location of tumour
Reference standard results blinded?	No	Only positive index test were subjected to the reference test
Index test results blinded?	Yes	"the results were blinded so that the two examinations were not linked"
Relevant clinical information?	Yes	Risk status of the patient was known, which would be the case in practice
Uninterpretable results reported?	Yes	These data are provided
Withdrawals explained?	Yes	"Eight women withdrew from the study before their first screening visit and another 35 were excluded because they ultimately were identified as non-mutation carriers in a *BRCA1/2* family"

Table App 1.5 Characteristics of included studies – Kuhl 2005

Kuhl 2005[63]	
Clinical features and settings	Women were recruited from a high-risk breast cancer clinic; included were women who were asymptomatic, but had an established lifetime risk of breast cancer of over 20%, with or without a personal history of cancer
Participants	529 women, mean age 41.7 ± 9.4 years - 139 personal history of breast cancer - 390 no personal history of breast cancer
Study design	Non-randomised prospective comparative cross-sectional cohort study
Target condition and reference standard(s)	Breast cancer Histologic evaluation of a biopsy specimen (positive index test) or by follow-up (negative index test)
Index and comparator tests	Mammography and MRI
Follow-up	Mean 5.3 years, range 2 to 7 years
Notes	

Table App 1.6 Assessment of methodological quality – Kuhl 2005

Item	Authors' judgment	Support for judgment
Representative spectrum?	Yes	Of the 529 participants, 21% had a lifetime risk of 20%, 46% had a lifetime risk of between 21% to 40% and 8% were confirmed mutation carriers
Acceptable reference standard?	Yes	Biopsy used to confirm positive index test result, negative tests were followed up to record interval cancers
Acceptable delay between tests?	Yes	"the three imaging studies were performed within a time frame of 8 weeks"
Partial verification avoided?	Yes	All positive index tests were biopsied, all negative index tests were followed up
Differential verification avoided?	No	The reference standard for positive results on index tests was a biopsy, for negative tests it was follow-up to monitor the incidence of new cancers
Incorporation avoided?	No	Biopsy relies on imaging test to identify location of tumour
Reference standard results blinded?	No	Only positive index tests were biopsied
Index test results blinded?	Yes	"The readers were informed about the clinical findings (CBE) and the risk status of the patient, but blinded to the results of the respective other imaging modalities."
Relevant clinical information?	Yes	Risk status of the patient was known
Uninterpretable results reported?	Yes	BI-RADS 3 on mammography and MRI were "managed by a short-term (6 months) follow-up until they received either a BI- RADS 2 category or were clarified by biopsy" "No BI-RADS 0 was assigned (assessment incomplete), because women were not recalled, but the entire diagnostic work-up (additional views, spot compression) was done ad hoc (i.e., immediately in case an abnormality was identified on the standard mammographic views)."
Withdrawals explained?	Yes	"590 women met the criteria of high familial risk. Of those, 12 patients presented with a clinical abnormality suggestive of breast cancer at their first visit"..."49 women underwent only one surveillance round and were lost to follow-up thereafter."

Table App 1.7 Characteristics of included studies – Leach 2005

Leach 2005[42]	
Clinical features and settings	Asymptomatic women at high risk of breast cancer; all participants had at least 2 annual scans; participants recruited over 6 years across 22 UK centres
Participants	649 women, range 31-55 years, median 40 years, 1 woman > 50 years.
Study design	Non-randomised prospective multicentre comparative cross-sectional cohort study
Target condition and reference standard(s)	Breast cancer Biopsy for positive index tests, follow-up to record interval cancers for negative tests
Index and comparator tests	MRI and mammography
Follow-up	From 1-7 annual screening events
Notes	

Table App 1.8 Assessment of methodological quality – Leach 2005

Item	Authors' judgment	Support for judgment
Representative spectrum?	Yes	Participants included genetic mutation carriers, 1st degree relative of a mutation carrier or people with a strong family history of breast or ovarian cancer
Acceptable reference standard?	Yes	Biopsy used to confirm positive index test result, negative tests were followed up to record interval cancers
Acceptable delay between tests?	Yes	"76% (1437 of 1881) of the CE MRI and mammography examinations were done on the same day, and only 4% (71 of 1881) were more than a month apart (maximum 184 days)."
Partial verification avoided?	Yes	All positive index tests confirmed by pathology, all negative index tests followed up
Differential verification avoided?	No	"For every woman in every year, we compared the CE MRI score and the mammography score (both double-read, taking the more conservative score) with her true cancer status, as ascertained by pathology (where a biopsy was taken) or by the absence or presence of an interval cancer in the year after the examination"
Incorporation avoided?	No	Biopsy relies on imaging test to identify location of tumour
Reference standard results blinded?	No	Only positive index tests biopsied
Index test results blinded?	Yes	"Radiologists unaware of the results of the other tests reported the findings of the screening studies."
Relevant clinical information?	Yes	"Once reported, the clinician taking responsibility for the screening event reviewed all the results of the diagnostic tests as an integrated whole, in the case of women recalled for additional tests or for surgical intervention."
Uninterpretable results reported?	Yes	Indeterminate results counted as positive
Withdrawals explained?	Yes	Flowchart provided

Table App 1.9 Characteristics of included studies – Warner 2004

Warner 2004[62]	
Clinical features and settings	*BRCA1/2* mutation carriers recruited across a number of familial cancer clinics in Canada, all testing done in one hospital.
Participants	236 women, mean age at first screening 46.6 years (26.4-64.8 years).
Study design	Non-randomised prospective comparative cross-sectional cohort study
Target condition and reference standard(s)	Breast cancer Biopsy and follow-up
Index and comparator tests	Annual MRI and Mammography
Follow-up	Annual questionnaire, all subjects were followed up to at least one year after last screening interval
Notes	

Table App 1.10 Assessment of methodological quality – Warner 2004

Item	Authors' judgment	Support for judgment
Representative spectrum?	No	Only women with *BRCA1/2* mutations were included. No participants had only a strong family history.
Acceptable reference standard?	Yes	Biopsy for positive index test, follow-up for negative index test
Acceptable delay between tests?	Yes	"All 4 were performed on the same day at the Sunnybrook campus of the Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario."
Partial verification avoided?	Yes	All results verified using either biopsy of follow-up
Differential verification avoided?	No	Different reference tests used depending on index test result
Incorporation avoided?	No	Index test result needed to locate tumour
Reference standard results blinded?	No	Only positive index test results were biopsied
Index test results blinded?	Unclear	"Each imaging study was read and scored independently by a different radiologist (P.A.C. and R.A.J.) who specialized in breast imaging. Radiologists were blinded to the results of the CBE." Blinded to clinical breast examination, but not specified if blinded to results of other index tests
Relevant clinical information?	Yes	Radiologist was aware of risk status
Uninterpretable results reported?	Yes	Mammography – "Further views were performed when judged to be necessary. Mammograms were scored on a 5-point scale, using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) categories (0=needs further work-up;..)" MRI - "Masses that were believed to be due to fibroadenomas or to intra-mammary lymph nodes, but could not be confidently classified as such, or asymmetric nonmass enhancements that did not fall into the previously mentioned categories, were classified as BI-RADS 3. Women with BI-RADS 3 lesions did not routinely undergo biopsy, but were followed up at

		6months, 1 year, and 2 years after the initial imaging study. If a lesion resolved, decreased, or remained stable during 2 years, it was reclassified as BI-RADS 2."
Withdrawals explained?	Yes	"A total of 205 women (87%) had a mammogram in the 15 months before starting the study. All women (100%) completed at least 1 round of screening, 136 (58%) completed at least 2 rounds, and 85 (36%) completed all 3 rounds. A total of 120 women are still undergoing annual screening. Thirty-one women left the study before completing all 3 rounds; 16 underwent bilateral mastectomy, 3 were too large to fit into the MRI machine, 3 stopped their participation due to pregnancy, 4 developed metastatic cancer, 4 were lost to follow-up, and 1 no longer wished to participate."

Table App 1.11 Characteristics of included studies – Sardanelli 2011

Sardanelli 2011[70]	
Clinical features and settings	Multicentre trial involving 501 women enrolled between June 2000 and Jan 2007 in 18 centres located in 14 towns in Italy.
Participants	501 asymptomatic women aged between 22 and 79 at high risk for breast cancer, selected for being (a) proven carriers of deleterious BRCA1 or BRCA2 mutations or untested first-degree relatives of BRCA1 or BRCA2 mutation carriers (i.e., 50% risk to be a carrier), or (b) having a strong family history of breast or ovarian cancer with 3 or more events in first- or second-degree relatives in either the maternal or paternal line. Patients may have had a personal history of breast cancer.
Study design	Non-randomised prospective multicentre comparative cross-sectional cohort study
Target condition and reference standard(s)	Breast cancer Biopsy for positive index tests, follow-up to record interval cancers for negative tests
Index and comparator tests	Annual CBE, mammography, ultrasonography and MRI for at least two screening rounds
Follow-up	100% at year 1, 85% at year 2, 67% at year 3, 46% at year 4
Notes	Data on the under 50 years subgroup is presented separately. Mammography method was a mixture of film and digital mammography

Table App 1.12 Assessment of methodological quality – Sardanelli 2011

Item	Authors' judgment	Support for judgment
Representative spectrum?	Yes	Asymptomatic women at high risk for breast cancer who were proven carriers of deleterious BRCA1 or BRCA2 mutations or had a strong family history of breast or ovarian cancer. General exclusion criteria were pregnancy, breast-feeding, current chemotherapy, terminal illness, and contraindications to MRI or gadolinium-based contrast agent administration.
Acceptable reference standard?	Yes	Biopsy used to confirm positive index test result, negative tests were followed up to record interval cancers
Acceptable delay between tests?	Unclear	Not reported, however an earlier report from the same trial indicated that for the first 377 patients time between tests ranged from same day

		to 8 weeks (For each of the 377 screening events, four examinations (CBE, mammography, US, and contrast enhanced MR imaging) were performed on the same day (n=347), during 1 week (n = 1), during 2 weeks (n = 15), during 3 weeks (n = 2), during 4 weeks (n = 2), during 5 weeks (n = 1), during 6 weeks (n = 2), during 7 weeks (n = 2), and during 8 weeks (n = 5).)
Partial verification avoided?	Yes	All positive index tests were biopsied, all negative index tests were followed up
Differential verification avoided?	No	The reference standard for positive results on index tests was a biopsy, for negative tests it was follow-up to monitor the incidence of new cancers
Incorporation avoided?	No	Biopsy relies on imaging test to identify location of tumour
Reference standard results blinded?	No	Only positive index tests biopsied
Index test results blinded?	Yes	"Forty-one radiologists interpreted the mammograms and 44 physicians performed and interpreted ultrasonography" "MR examinations were interpreted by 30 radiologists". The earlier report from this study stated "Each reader was ... blinded to the results of the other three diagnostic modalities. During the second round, the readers were aware of the results from the first annual round."
Relevant clinical information?	Yes	Each reader was aware of the high-risk condition of the women
Uninterpretable results reported?	Yes	Indeterminate test results provided in tables
Withdrawals explained?	Yes	"voluntary withdrawal or loss at follow-up (n=227), prophylactic bilateral mastectomy (n=19), screen-detected or interval breast cancer (n=15), other diseases (n=10), or onset/evolution of concurrent ovarian malignancy (n=2)."

Table App 1.13 Summary of additional studies

Study Name	Country	N	Imaging Modality	Frequency of screening	Follow-up	Sensitivity	Specificity
Pisano 2008[78]	United States and Canada	42,760	FMX	Annual	1 year	0.44 [0.33, 0.57]	0.90 [0.90, 0.91]
			DMX			0.68 [0.56, 0.79]	0.90 [0.90, 0.91]

Table App 1.14 Characteristics of additional studies – Pisano 2008

Pisano 2008[78]	
Clinical features and settings	Women attending for screening at 33 sites in the USA and Canada
Participants	42,760 women, mean age 54.9, interquartile range, 47-62
Study design	Non-randomised prospective multicentre comparative cross-sectional cohort study
Target condition and reference standard(s)	Breast cancer Biopsy for positive tests, follow-up for negative tests
Index and comparator tests	Film and digital mammography
Follow-up	455 days
Notes	Population was not classified as being at elevated risk

Table App 1.15 Assessment of methodological quality – Pisano 2008

Item	Authors' judgment	Support for judgment
Representative spectrum?	No	Enrolment was not limited to women at increased risk of breast cancer
Acceptable reference standard?	Yes	Biopsy for positive test results, follow-up for negative results
Acceptable delay between tests?	Unclear	"When indicated, percutaneous and/or surgical biopsy was performed after the work-up was completed."
Partial verification avoided?	Yes	All positive index tests confirmed by pathology, all negative index tests followed up
Differential verification avoided?	No	Different reference tests used depending on index test result
Incorporation avoided?	No	Index test result needed to locate tumour
Reference standard results blinded?	No	Only positive index test results were biopsied
Index test results blinded?	Yes	"Each pair of digital and screen-film mammograms were independently interpreted at the sites where they were acquired by two radiologists, one for the digital study and one for the

		screen-film study of each subject, within 7 days of each other and without consultation."
Relevant clinical information?	Yes	"Both readers had access to the same information about the participant, including prior studies for comparison, if available, and demographic information and medical history."
Uninterpretable results reported?	Yes	BI-RADS 0 results were reported
Withdrawals explained?	Yes	"A total of 49,528 women were enrolled in the trial. Of these, 195 (0.4 percent) were subsequently determined to be ineligible and 194 (0.4 percent) withdrew from the study. In addition, 1,489 women (3.0 percent) were excluded from the analysis because the study protocol had not been followed at one participating institution, as determined by on-site audits."

App 1.16 Excluded studies comparing MRI and mammography in women at an elevated risk of breast cancer

Study	n	Age range	Risk classification	Positive test result	False negative identification	Reason for exclusion
Kriege 2004[60]	1,909	25-70	Cumulative lifetime risk of breast cancer of 15% or more owing to a familial or genetic predisposition, according to the modified tables of Claus, and an age of 25 to 70 years. Women could be screened at an age younger than 25 if they had a family history of breast cancer diagnosed before the age of 30 years, since screening began at an age 5 years younger than that at which the youngest family member was found to have breast cancer.	BI-RADS 0,3,4,5	A test result is a false negative when a proven cancer (diagnosed on the basis of a histologic examination) is detected in the interval between annual testing or by one of the other methods.	Age > 65
Warner 2001[151]	196	25-59	Age 25 to 60 and at high risk for breast cancer because of either (1) a germline *BRCA1* or a *BRCA2* mutation, (2) a first-degree relative with a *BRCA1* or *BRCA2* mutation (but an unknown personal mutation status), or (3) three or more relatives on the same side of the family with breast cancer diagnosed before age 50 or ovarian cancer. A woman with a past history of unilateral breast cancer who satisfied the criteria was also eligible if her contralateral breast had not been removed.	BI-RADS 4,5	Interval cancers and proven positive test results identified by an alternative test	Subset of Warner 2004[62]
Riedl 2007[152]	327	22-80	Women with a positive test result for a germ-line *BRCA1* or *BRCA2* mutation; women with (a) three or more relatives on the same side of the family with breast cancer diagnosed before the age of 61 or one relative diagnosed with ovarian cancer at any age, (b) two or more relatives on the same side of the family with breast cancer diagnosed	BI-RADS 4,5	Interval cancers and proven positive test results identified by an alternative test	Age > 65

			before the age of 51 or one relative diagnosed with ovarian cancer at any age, and (c) a relative with breast cancer diagnosed before the age of 36. In any case, the women had to be a first-degree relative of one of the affected relatives or be one of the affected herself. Women had to be of age 25 or older, but could also be included at a younger age because surveillance was recommended to begin at an age 5 years younger than the youngest incidence of breast cancer in that family.			
Hagen 2007[153]	491	18-79	Women found to have a truncating mutation in either *BRCA1* or *BRCA2* genes	BI-RADS 3,4,5	Interval cancers and proven positive test results identified by an alternative test	Age > 65
Trop 2010[154]	184	21-75	Women who were either known carriers of *BRCA1* mutations or, if they had declined genetic testing, were known to have a family history of mutation with at least a 30% risk of being a carrier as calculated by BRCAPRO software.	BI-RADS 4,5	Biopsy proven positives identified by an alternative test	Age > 65
Weinstein 2009[74]	609	25-80	Women between the ages of 25 and 80 years who were considered at high risk for breast cancer based on any of the following were considered eligible: positive test for a mutation in *BRCA1* or *BRCA2*, >25% lifetime risk based on the Claus or Gail models, previous diagnosis of lobular carcinoma in situ or atypical hyperplasia (atypical ductal hyperplasia or atypical lobular hyperplasia), history of chest wall radiation before puberty, and a recent diagnosis of breast cancer in the contralateral breast. In participants with recent diagnosis of breast cancer, only the data from the cancer-free breast were included in the study.	BI-RADS 0,3,4,5	Biopsy proven positives identified by an alternative test.	Age > 65

Trecate 2006[155]	116	23-81	The following entrance criteria were used: 1) *BRCA1* or *BRCA2* gene mutations or with a 1:2 probability to be mutation carriers; 2) individuals with a positive personal history for breast or ovarian cancer 3) individuals at high risk (>50%) of carrying a susceptibility gene for familial breast cancer on the basis of familial history: a) at least 3 cases of breast cancer before 60 years of age in first or second-degree relatives or b) at least 3 cases of breast cancer before 60 years of age and ovarian cancer at any age; or c) at least 3 cases of breast cancer before 60 years of age and male breast carcinoma at any age.	Not Defined	Biopsy proven positives identified by an alternative test.	Age > 65
Kuhl 2000[33]	192	18-65	A personal history or a history of a relative with breast cancer diagnosed at or before the age of 35 years; a personal history or a history of a relative with ovarian cancer diagnosed at or before the age of 40 years; a personal history or a history of a relative with bilateral breast cancer; a personal history or a history of a relative with both breast and ovarian cancers; a history of at least two relatives with breast and/or ovarian cancer, one of whom received a diagnosis at or before the age of 50 years; or a man with a personal history of breast cancer or a history of a male relative with breast cancer.	BI-RADS 4,5	Biopsy proven positives identified by an alternative test	Subset of Kuhl 2005[63]

Bigenwald 2008[156]	507	25-65	Patient eligibility was restricted to women unaffected or with a past history of breast cancer who (a) were known *BRCA* mutation carriers, (b) were untested first-degree relatives of a *BRCA* mutation carrier, or (c) had three relatives on the same side of the family with breast cancer diagnosed before age 50 or epithelial ovarian cancer.	BI-RADS 4,5	Cancers detected by one modality that were not detected by another.	Not possible to identify false negatives that tested negative on both tests; unable to calculate specificity
Berg 2012[107]	2809	25-91	Study participants included women who were asymptomatic, presenting for routine annual mammography with heterogeneously dense or extremely dense breast tissue and who had at least 1 other risk factor for breast cancer	BI-RADS 3,4,5	Interval cancers and proven positive test results identified by an alternative test	Age > 65 and study design does not compare MRI and mammography directly

Appendix 2 – Reviews

App 2.1 Systematic review of cost-effectiveness analyses

A systematic review of the literature was conducted to identify and assess existing studies of the cost-effectiveness of breast cancer surveillance in women aged less than 50 at elevated risk of developing breast cancer. The search was conducted in the PubMed and Embase databases in January 2012. The results flow chart and the Embase search strategy are reported in figure App2.1 and table App 2.1, respectively.

The search yielded 141 unique abstracts. These were hand sorted independently by two reviewers, resulting in seven relevant papers from which necessary information could be extracted. The principal characteristics and main results of these seven studies are recorded in Chapter 5, Table 5.1.

Figure App 2.1 Results Flow Chart

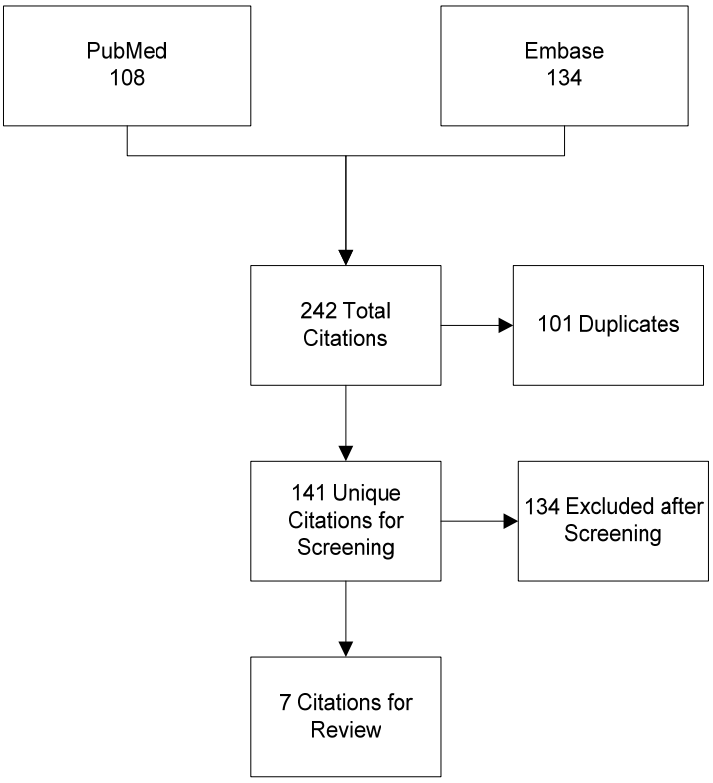


Table App2.1 Embase search strings

Embase search	
1	breast.ti,ab.
2	mammary.ti,ab.
3	1 or 2
4	cancer.ti,ab.
5	carcinoma$1.ti,ab.
6	neoplasm$1.ti,ab.
7	tumo?r$1.ti,ab.
8	lesion$1.ti,ab.
9	metasta$.ti,ab.
10	or/4-9
11	3 and 10
12	diagnos$.ti,ab.
13	screen$.ti,ab.
14	surveillance.ti,ab.
15	detect$.ti,ab.
16	test$3.ti,ab.
17	or/12-16
18	mri.ti,ab.
19	magnetic resonance imaging.ti,ab.
20	mr imaging.ti,ab.
21	zeugmatography.ti,ab.
22	mammogra$.ti,ab.
23	ffdm.ti,ab.
24	or/18-23
25	high$ risk.ti,ab.
26	increased$ risk.ti,ab.
27	elevat$ risk.ti,ab.
28	brca$.ti,ab.
29	family history.ti,ab.
30	first degree relative.ti,ab.
31	blood relative.ti,ab.
32	genetic.ti,ab.
33	inherited.ti,ab.
34	familial.ti,ab
35	hereditary.ti,ab.
36	or/25-35
37	cost-effective$.ti,ab.
38	cost-utility.ti,ab.
39	comparative-effectiveness.ti,ab.
40	economic$.ti,ab.
41	or/37-40
42	**11 and 17 and 24 and 36 and 41**

Description of reviewed studies

Griebsch et al. (2006)[119] conducted a trial-based cost-effectiveness analysis (CEA) of annual mammography, MRI and mammography plus MRI. The study group were participants of the UK MARIBS trial, who were either *BRCA1* or *BRCA2* or *TP53* mutation carriers or women with a strong family history of breast cancer. Women were recruited to the trial between the ages of 35 and 49 years and received between one and seven screens over seven years of follow-up. The outcomes recorded in the study were the number of cancers detected. The study did not include treatment costs. Consequently, it is difficult to compare this study to others that estimate final health outcomes. The incremental cost of detecting a cancer with mammography plus MRI relative to mammography alone was £28,300 in all women and was £15,300 in *BRCA2* mutation carriers. All strategies were more cost-effective when the analysis was restricted to the prevalent screens alone.

Moore et al. (2009)[157] used a Markov cohort model to assess the cost-effectiveness of annual mammography and annual MRI in US women from age 25 with a cumulative lifetime risk of breast cancer of 15% or more. The cost-effectiveness of mammography in combination with MRI was not assessed. The ICER of MRI relative to mammography was estimated to be $179,600/QALY. The baseline comparator used in the model was not sufficiently described to provide a useful estimate of the cost-effectiveness of mammography alone.

Taneja et al. (2009)[118] estimated the cost-effectiveness of mammography, MRI, and mammography plus MRI in *BRCA1* or *BRCA2* mutation carriers in the US. The model description states that women received one screen, which occurred on entry into the model at age 40, but also mentions that screening histories were assumed to match clinical trials. Consequently, it is unclear if the single screen modelled represents a prevalent screen or a screen after a given interval. They found that MRI alone was subject to extended dominance. The estimated ICER of adding MRI to mammography was $45,600 for the *BRCA1* and *BRCA2* risk groups combined. The cost-effectiveness of mammography alone was not reported.

Lee et al. (2010)[115] estimated the cost-effectiveness of mammography, MRI and mammography plus MRI in *BRCA1* mutation carriers in the US. They modelled annual screening from age 25 onwards using a probabilistic Markov model. A screening stop age is not stated for the model, nor did it consider any alternative screening start ages. The cost-effectiveness of annual mammography was estimated to be $16,800/QALY relative to no screening. MRI was subject to extended dominance. Mammography plus MRI was estimated to have an ICER of $69,100/QALY.

Norman et al. (2007)[120] considered the cost-effectiveness of mammography, MRI and mammography plus MRI in *BRCA1* mutation carriers in the UK. They used a Markov cohort model to estimate the cost-effectiveness of 10 years of screening initiated either between the ages of 30-39 or 40-49. The mortality benefit of screening was modelled by assuming a reduction in five-year mortality rates for screen-detected cancer, but that this benefit reduced with the number of screening rounds at which a given cancer was missed. The estimated results showed MRI alone to be subject to extended dominance in both age groups. In the younger age group, annual mammography had an ICER of £5,200/QALY relative to no screening, while adding MRI had an ICER of £13,500/QALY; both strategies were found to be more cost-effective in the older age group at £2,900/QALY and £7,800/QALY, respectively.

Grann et al. (2011)[158] considered the cost-effectiveness of a range of preventive interventions including prophylactic organ removal and chemoprevention in addition to surveillance in *BRCA1* or *BRCA2* mutation carriers. They used a probabilistic Markov model to assess surveillance with annual mammography and mammography plus MRI from age 30 to 65 and the other interventions. The analysis does not provide or facilitate an estimate of mammography alone compared to no surveillance. Excluding prophylactic surgery and chemoprevention, the ICER of mammography plus MRI relative to mammography was estimated at $116,400/QALY and $67,600/QALY for *BRCA1* and *BRCA2* mutation carriers, respectively. The rank ordering of these ICERs appears counter-intuitive as mammography plus MRI appears to be less cost-effective in the higher risk *BRCA2* group.

Plevritis et al. (2006)[117] estimated the cost-effectiveness of adding MRI to mammography at different start and stop ages for carriers of *BRCA1* or *BRCA2* mutations in the US. They used a probabilistic Markov model to compare adding MRI at various ages between 25 and 69. The model was one of the more detailed of those reviewed, with tumours within the natural history model differentiated by size and grade and the mortality benefit of screening estimated with respect to observed survival by tumour stage and grade, with adjustments made for screen-detection and the use of adjuvant therapy. They reported a range of cost-effectiveness estimates along an efficient frontier of strategies. In both *BRCA1* and *BRCA2* mutation carriers restricting the addition of annual MRI to surveillance mammography ages 40-49 was found to be the most cost-effective option at ICERs of $43,500/QALY and $111,600/QALY, respectively. Adding annual MRI over the complete 25-69 age group resulted in very high ICERs of $475,900/QALY and $731,600/QALY for *BRCA1* and *BRCA2* mutation carriers, respectively. The cost-effectiveness of annual mammography alone between ages 25-69 years was also reported as $19,000/QALY and $28,400/QALY for *BRCA1* and *BRCA2* mutation carriers, respectively.

Comments

There is considerable variation within the seven studies regarding model design, risk subgroups analysed and surveillance strategies compared. Consequently, there are few directly comparable results. While there appears to be little consensus in terms of cost-effectiveness estimates, the extended dominance of MRI screening only by mammography and mammography plus MRI is found in several studies.

Of the seven studies reviewed, six were model-based analyses. The degree of detail of the models varied between studies. For example, some models differentiated disease by tumour size, grade and lymph node involvement while others did not disaggregate disease stages. Other areas of methodological variation included the estimation of the reduction in mortality from screening and handling of competing risk of other cause mortality. However, it is unclear if more detailed models lead to more accurate cost-effectiveness estimates.

Of the seven studies reviewed, five were from the US. The US studies tended to assess annual breast imaging from a relatively young age of 25 until the late 60s or older. Consequently, the relatively high ICERs of adding MRI to mammography from the US studies may, in part, be a consequence of the early starting ages of the surveillance programmes. In this respect, Plevritis et al. represents one of the most useful studies, as it considers a range of ages over which MRI might be added to mammography. Their results show that the ICER of adding MRI to mammography over the 40-49 age range is considerably lower than the ICER of adding MRI over a range of 25-69.

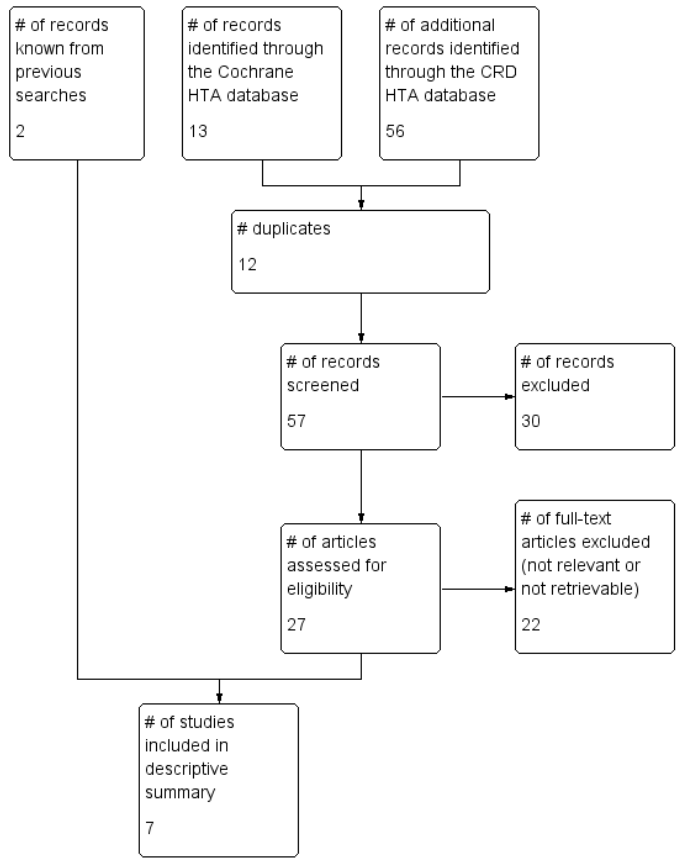
Comparing Plevritis et al.'s estimate[117] for adding MRI between ages 40-49 years in the US to Norman et al.'s estimate[120] of adding MRI for women of the same age range in the UK shows a very large difference in the estimates. A possible explanation for part of the difference is that the estimate of mammography sensitivity used by Plevritis et al. is low at 25%, while Norman et al. used an estimate of 40%.

It is significant that none of the reviewed studies assessed digital mammography. Norman et al. noted that digital mammography can have markedly higher sensitivity than conventional film mammography, citing sensitivities of 51% and 78% for screen and digital mammography, respectively. Given the sensitivity of cost-effectiveness to test sensitivity, the cost-effectiveness estimates of mammography alone from the reviewed literature are likely to be inferior to what digital mammography would achieve. Conversely, the cost-effectiveness of adding MRI to digital mammography is likely to be less favourable than the estimates for film mammography described above.

App 2.2 Review of published HTAs

A search of the Centre for Reviews and Dissemination (CRD) database of HTAs and the Cochrane HTA database was carried out in December 2012 for published technology assessments carried out in other countries evaluating systematic programmes for the detection of breast cancer in woman at elevated risk of developing the disease. The search is outlined in table 1.

Table App 2.2 HTA search details



Database	search details
Cochrane HTA database	(Breast Neoplasms[Mesh]) AND (Mass Screening[Mesh]) AND (Diagnosis[Mesh]) AND (risk ti:ab:kw)
CRD HTA database	(breast) AND (surveillance OR screening OR detection OR diagnosis) AND (risk)

Many of the reports identified dealt with slightly different populations or diagnostic test comparisons than those of interest to this assessment. In addition, several were completed prior to the availability of some of the more recent research results that are included in this analysis. Despite these limitations, a summary of the conclusions reached by previous HTAs in this area is useful for providing context in relation to how questions were framed in other health systems and the conclusions that were reached. A summary of identified studies is provided below

Study	Title	Population	Diagnostic Test(s)	Conclusions
Mundy 2004[159] **(Australia and New Zealand Horizon Scanning Network)**	MRI Screening for Breast Cancer in Genetically High-Risk Women	Asymptomatic women without a history of breast cancer Asymptomatic women with a history of breast cancer Asymptomatic women at high risk of breast cancer	MRI in addition to mammography for genetically high risk women	'MRI appears to be of benefit in the diagnosis of women at high-risk of developing breast cancer. MRI appears to have improved sensitivity, comparable false-positive rates and improved false-negative rates when compared to mammography, for young, at risk women.'
	Systematic Review of Evidence	**Cost-effectiveness analysis**	**Other**	
	Yes	Limited review of CEA data from previous studies; estimated 2004 unit costs in Australia	Brief ethical analysis Training and credentialing discussed	

Study	Title	Population	Diagnostic Test(s)	Conclusions
Dunfield 2007[160] **(Canadian Agency for Drugs and Technologies in Health)**	Effectiveness of magnetic resonance imaging (MRI) screening for women at high risk of breast cancer	Women at high risk of developing breast cancer	MRI versus film mammography in women at high risk of breast cancer	'The cost-effectiveness studies suggest that MRI for breast cancer screening could be cost effective, depending on the willingness to pay and the value attributed to one QALY. Overall, MRI has a higher sensitivity for breast cancer screening compared to mammography. The number of cancers detected by MRI alone was higher than that detected by mammography alone, although MRI also missed some cancers. These results indicate that some breast cancers would have been missed with mammography screening alone and the addition of MRI resulted in more cancers being detected. High-risk women, such as those with *BRCA1/2* mutations, those having a first-degree relative with a mutation, or those with a strong family history of breast cancer, seem to benefit most from the addition of MRI to the screening modality.'
	Systematic Review of Evidence	**Cost-effectiveness analysis**	**Other**	
	Yes	Summary of limited CEA data from other studies. No new economic analysis.	No	

Study	Title	Population	Diagnostic Test(s)	Conclusions
Davidson 2007[161] **(New Zealand Health Technology Assessment)**	Surveillance of Women at High Risk of Breast Cancer	Women at high risk of breast cancer	Comparison of accuracy and outcome of MRI, Mammography and Ultrasound surveillance compared to usual care	'MRI alone or in combination with other surveillance modalities appears to be a promising strategy for the surveillance of women at high risk of breast cancer. However, there is no evidence currently to suggest that such surveillance will necessarily translate to a decrease in mortality among this population. More research with larger numbers of participants and longer follow-up is required to truly assess the performance of MRI and combination strategies for the surveillance of women at high risk of breast cancer. In addition to its accuracy, MRI has the advantage of not using ionising radiation. The drawbacks of MRI are primarily related to the potential harm of false-positive diagnoses, cost and availability. If the introduction of a surveillance strategy for women at high risk of breast cancer with MRI was to be contemplated, a more complete assessment would need to be carried out. This should include the potential benefit from surveillance versus the potential physical and psychological harm caused by the test, diagnostic procedures and treatment; the health care system being capable of supporting all the necessary elements of the surveillance pathway, including diagnosis, follow-up and evaluation; consideration of social and ethical issues and consideration of cost-benefit issues.'
	Systematic Review of Evidence	**Cost-effectiveness analysis**	**Other**	
	Yes	None	No	

Study	Title	Population	Diagnostic Test(s)	Conclusions
AETSA 2006[162] **(Health Technology Assessment Agency of Andalucía)**	Magnetic Resonance imaging for breast cancer diagnostics. Systematic review and economic assessment.	Women with a genetic predisposition to breast cancer Women with suspected breast cancer	MRI compared to existing standard of care (including mammography and ultrasound) for a range of indications (e.g. screening high risk women, diagnosis of suspected cancer, staging, assessing results of neoadjuvant chemotherapy)	'MRI is effective as a screening method in women with a genetic predisposal to breast cancer. There is insufficient evidence to determine if its safety is better than that of the other alternative tests. The studies retrieved do not allow drawing valid conclusions on whether MRI can be used complementarily to mammography when the sensitivity of the latter is hindered by the characteristics of the breast (dense breast, post-surgical scars, or radiotherapy). All contrast agents based on gadolinium are similar as regards to effectiveness and safety. As there is no dominance between the alternatives, it is necessary to establish a decision criterion on the willingness to pay per unit of additional effect gained. The results obtained from this analysis are widely under the threshold considered as cost effective in Spain.'
	Systematic Review of Evidence	**Cost-effectiveness analysis**	**Other**	
	Yes	Includes original CEA of 1)mammography only; 2)mammography and ultrasound; 3) mammography and MRI. ICER of mammography+MRI strategy is €255,355/ additional LYG with respects to mammography only.	Analysis of patient preferences	

Study	Title	Population	Diagnostic Test(s)	Conclusions
MAS 2010[111] **(Medical Advisory Secretariat, Ontario)**	Cancer Screening with Digital Mammography for Women at Average Risk for Breast Cancer, Magnetic Resonance Imaging (MRI) for Women at High Risk	Women at average and increased risk of breast cancer	Effectiveness of screening with MRI and digital mammography versus film mammography in high risk women with no previous history of breast cancer	'There is moderate quality evidence that DM is significantly more sensitive than FM in the screening of asymptomatic women aged less than 50 years, those who are premenopausal or perimenopausal, and those with heterogeneously or extremely dense breast tissue (regardless of age). It is not known what effect these differences in sensitivity will have on the more important effectiveness outcome measure of breast cancer mortality, as there was no evidence of such an assessment. Other factors have been set out to promote DM, for example, issues of recall rates and reading and examination times. Our analysis did not show that recall rates were necessarily improved in DM, though examination times were lower than for FM. Other factors including storage and retrieval of screens were not the subject of this analysis.'
	Systematic Review of Evidence	**Cost-effectiveness analysis**	**Other**	
	Yes	Review of literature and original analysis. Conclusion: breast MRI plus mammography is a cost-effective strategy for high risk women and the estimated budget impact is $7- $27M annually, based on the predicated uptake rate.	Policy analysis Training and credentialing discussed	

Study	Title	Population	Diagnostic Test(s)	Conclusions
MSAC 2006[163] **(Medical Services Advisory Committee, Australia)**	Breast magnetic resonance imaging	Asymptomatic high-risk women under the age of 50 years and in those aged 50 years and older	MRI as an addition or replacement to mammography with or without breast ultrasound for screening	'Breast MRI, when combined with mammography, is safe and effective in the diagnosis of breast cancer in asymptomatic women at high risk, when used as part of an organised surveillance program. Evidence suggests that breast MRI in combination with mammography may be cost-effective when compared with mammography alone in high risk women aged less than 50 years.'
	Systematic Review of Evidence	**Cost-effectiveness analysis**	**Other**	
	Yes	CEA concluded that based on modelled estimates of the effects of early detection, MRI may be cost-effective for screening women at very high-risk such as *BRCA1* mutation carriers aged 35-54 years, but is unlikely to be cost-effective for screening *BRCA2* carriers or women with a wider risk or age distribution.	No	

Study	Title	Population	Diagnostic Test(s)	Conclusions
MSAC 2007[164] **(Medical Services Advisory Committee, Australia)**	Digital mammography for breast cancer, screening, surveillance and diagnosis	Asymptomatic women at average or high risk and women with symptoms of breast cancer	To evaluate the use of digital mammography in screening of the general population, surveillance of high risk women and in the diagnosis of women with signs or symptoms of the disease in order to determine if digital mammography should either replace, be used as an alternative or be used in addition to film mammography	'MSAC finds that digital mammography is as safe and as effective [as film mammography]. There may be subgroups of patients where it is more effective. Film mammography is being superseded by digital mammography and will lose technical support. MSAC recommends that public funding is supported for this procedure under the arrangements that currently apply to film mammography.'
	Systematic Review of Evidence	**Cost-effectiveness analysis**	**Other**	
	Yes	CEA of digital versus film mammography concluded that the incremental cost per digital mammogram in a surveillance of women at high risk setting was AUD€11-€36, with an incremental cost per additional cancer detected of AUD€10,000	No	

Appendix 3 – Cost estimates

App 3.1 Cost of surveillance

The imaging options considered for surveillance in this HTA were digital mammography and magnetic resonance imaging (MRI). In the absence of a national database, cost data were sought from a number of sources in order to provide a best estimate of the cost to the Health Service Executive (HSE) of providing this imaging. Data was obtained from regional cancer centres, the National Procurement Office (NPO) in the HSE, BreastCheck and from the Scottish and English NHS systems.

Discussion with the NPO in the HSE revealed a number of salient points critical to the accurate determination of the cost of digital mammography and MRI to the HSE. It was highlighted that in recent years, the HSE has changed its procurement process, so that all new diagnostic imaging equipment and subcontracted imaging services are now procured through national framework agreements. There is little homogeneity across different hospital locations in respect of MRI equipment, its specification, functionality and use or in respect of the staffing mix. Many diagnostic imaging units are currently operating with a mixture of internal and external staff and some operate as externally managed services. Some hospitals have fully managed equipment service (MES) models in use, where the service provider provides a combination of equipment, staff, the facility itself (portable units etc.), and soft facilities management services, with the hospital paying only a cost per scan. There are also hybrid models where the hospital provides the facility, some of the staff and the soft facilities management service aspects, but the service provider provides the equipment. Many MES and hybrid models also include an element of private work which reduces the costs for public patients. Costing models do not differentiate between types of MRI scan (use of contrast enhancement, location, number of areas scanned) – rather procurement costs reflect an average price of an MRI scan. Through the national framework agreements, it is estimated that the cost of an MRI has been reduced by 30% to 40%. However, these changes mean that there is substantial variability in imaging costs as each hospital will have significantly different cost structures and cost elements making up the price of a scan.

Cost estimates for MRI and digital mammography were also supplied by finance departments from a number of regional cancer centres. This data was complied as part of Casemix submissions. Costs at a hospital level comprise the cost of all consumables used in providing the image, staff time, maintenance of equipment and allocated overhead costs. Costs for capital expenditure are excluded as equipment is procured through one-off capital grants from the HSE. Again, there is currently no differentiation between the types of MRI scan provided; instead the cost reflects an

average price of an MRI scan at that facility. The majority of digital mammography provided at the regional cancer centres is for the symptomatic services. In contrast to screening or surveillance mammography that consists, as a standard, of four low-dose X-rays (two per breast), a diagnostic mammogram may include additional views, such as spot compression or magnification views in order to investigate the finding in question. Costs cited for digital mammography and MRI ranged from €48-€169 and from €102-€161, respectively excluding capital costs.

BreastCheck, the national breast screening programme, provides over 120,000 screening mammograms per annum to women aged 50 to 64 years. Consistent with the mammography provided for the symptomatic services in publicly funded hospitals, the service is fully digitalised. The cost of screening is directly related to the number of women who attend for screening in a particular year and can fluctuate depending on the uptake rate. The estimate comprises all costs associated with the provision of a digital mammogram with the exception of capital equipment costs. Based on attendance in 2011, the estimated average cost of a screening mammogram (excluding capital costs) through BreastCheck was €92.50. The cost of digital mammography equipment provided to BreastCheck was obtained from the NPO in the HSE and the annual capital cost calculated based on a straight-line depreciation of the equipment over seven years. When combined with data on the average usage per machine by BreastCheck, the added capital cost for an image was estimated at €8 to give a final average cost of a digital mammogram of €102.50.

Given the uncertainty regarding the average cost of digital mammography and MRI to the HSE, cost data were also obtained from the NHS Scotland which publishes annual comprehensive data on the cost of its service.[165] Data include national average weighted costs, costs by facility and region, and a breakdown of costs into staffing, supplies and allocated costs; cost of capital equipment is also included. After converting to euro using Purchasing Power Parity, the average cost for MRI and digital mammography (provided as part of a screening service) were €218 and €91, respectively. Up to a 10-fold variation in the cost of an MRI was noted between hospitals, possibly reflecting local and regional variation in the type of scans provided and comparable issues to those seen in the HSE where more competitive cost structures have been obtained for more recent investments.

Cost data for MRI and digital mammography were also sought from English NHS Trusts which publishes annual comprehensive cost data for its service. Data for mammography are not listed on the NHS reference costs site.[139] However, MRI cost data are listed with differential costs provided according to the number of sites imaged (1, 2, 3, >3), the use of contrast enhancement (no contrast, post-contrast only, or pre- and post-contrast) and the complexity of the imaging (extensive patient repositioning, more than one contrast agent etc.). After converting to euro using

Purchasing Power Parity the average cost of an MRI with pre- and post-contrast images provided in an outpatient setting was €211.

An alternative approach of micro-costing was used to determine the typical price of a breast MRI in Ireland. The main components used to establish the cost were: the capital cost of the MRI machine; annual maintenance fees; lifespan of the machine; the number of breast scans that could be completed in a year; the cost of contrast per scan; the cost of two radiographers; the cost of a radiologist to read an image. It was established that the MRI equipment in place at present is a mix of 1.5T and 3T machines, with the majority being 1.5T. A range of prices were gathered from recent procurement processes, including the costs associated with building works, software, and equipment upgrades. Maintenance costs were also determined and applied from year 2 onwards, as the first year was covered under warranty. The HSE depreciates MRI equipment over 10 years. From a regional cancer centre it was estimated that 4,750 20 minute scans can be processed per annum on a single machine. It was determined that a breast scan is generally booked to last 60 minutes, suggesting that 1,583 breast scans could be processed per annum. This figure is similar to an estimated 1,777 scans in a Welsh costing study.[166] It was assumed that two radiographers would be present at all times and that it would take a consultant radiologist 15 minutes to read a study. The cost was estimated to be €259 per breast MRI. When VAT was applied to equipment, maintenance and contrast for the budget impact assessment, the cost was estimated at €289 per scan.

Table App 3.1 Cost components of breast MRI

Component	Value (ex-VAT)
Cost of MRI equipment (incl. maintenance) (€)	1,769,044
Lifespan (years)	10
Breast scans per annum	1,583
Contrast per scan (€)	18
Radiographer cost (per scan) (€)	86
Radiologist cost (per scan) (€)	43
Cost per scan (€)	259

Based on the quantity and quality of information available a decision was made to use the BreastCheck data for the cost of a digital mammogram, adjusting this figure for the capital cost. For an MRI scan, it was decided to use the Irish micro-costing data with an estimated cost of €259 per scan.

App 3.2 Cost of managing breast cancer in Ireland

The cost of managing breast cancer is country-specific and depends on the structure and cost base of the healthcare system within which care is provided. An essential component of this HTA was to establish the cost of managing breast cancer in Ireland by identifying the resources consumed and the cost of those resources.

There is no national cost database in Ireland. Cost estimates were therefore estimated from a variety of sources. Although data exists regarding the type of resources used (e.g., the proportion of patients receiving surgery, chemotherapy or radiotherapy), specific details on the exact type of each treatment used is not centrally documented. Assumptions were therefore made regarding use informed by hospital protocols and expert clinical opinion. As a result of the limitations of the cost data and the required assumptions for the resource use, there is considerable uncertainty regarding the overall estimates of the direct medical cost of breast cancer. This uncertainty was explored in sensitivity analyses, with all costs allowed to vary by +/- 20% in the economic model. Consistent with national guidelines, all costs were discounted at 4%.

The cost of managing breast cancer includes the cost of diagnosis and treatment. Costs associated with diagnostic imaging, biopsy, pathology, hospitalisation, surgery, radiotherapy, chemotherapy, supportive care, clinician visits, laboratory costs, ancillary medications and imaging were considered. As there are a range of options available for diagnosis and treatment of breast cancer, it was necessary to establish which are used in Ireland and for what proportions of patients. Resource use estimates based on data from a number of sources including the National Cancer Registry Ireland (NCRI), data from regional cancer centres, clinical guidelines and expert clinical opinion were used. Table 5.4 in Chapter 5 outlines the percentage of patients receiving each treatment type by stage of diagnosis; the majority of patients receive more than one treatment type (e.g., women with stage I, II and III breast cancer will typically receive primary locoregional treatment consisting of surgery and radiotherapy and adjuvant therapy [chemotherapy and, or endocrine therapy]). In the model, the percentage of patients receiving each kind of treatment was fluctuated using a beta distribution. For example, the percentage of patients with DCIS receiving mastectomy was 46% with a 95% CI of 33% to 60%.

Following a diagnosis of breast cancer, patients were assumed to be in active treatment for 12 months after which point they were assumed to return to active surveillance. It was assumed that women presenting with stage IV cancer who do not survive to five years will survive for one to three years (median two years). Management of these women was categorised into three phases: active treatment and follow-up; active supportive care (e.g. radiotherapy, transfusions); and end-of-life care (e.g., hospice, hospitalisation) using a model developed by Remak et al..[135]

It was assumed that all patients not surviving to five years would pass through these final two phases prior to death, with the mean duration of these phases estimated at 4.0 months and 0.47 months, respectively. All other time was assumed to be spent in the active-treatment and follow-up phase. It was assumed that women with stage I to III cancer who do not survive to five years initially go into remission before developing stage IV cancer in the final year of survival. These women receive stage IV treatment and subsequently active support and end-of-life care in that final year with again a mean duration of 4.0 months and 0.47 months estimated for active support and for end-of-life care. The resource use and cost of active support and end-of-life care was adapted from the Remak study[135] as there was a lack of Irish data to document the resource consumption by this cohort, particularly in relation to end-of life and active support care. All costs associated with the active support and end-of-life care phases were inflated to 2011 cost and transferred to euro using Purchasing Power Parity.

App 3.2.1. Unit cost data

The unit cost data included in the model are summarised in Chapter 5, Table 5.7. Unit cost for radiotherapy was estimated using Diagnostic Related Group (DRG) costs. Unit costs for diagnostic procedures and laboratory tests were obtained from hospital finance departments in a number of regional cancer centres and are based on Casemix and patient-level costing exercises conducted in those institutions. Every effort was made to incorporate Irish unit cost data – where unavailable, cost data was adapted from the UK. In accordance with existing guidelines for the conduct of economic evaluations, all retrospective costs were inflated to 2011 using the consumer price index for health with costs transferred to euro using the Purchasing Power Parity as necessary.

Diagnosis

Following a reported abnormal surveillance result, all women were assumed to be recalled to a radiological assessment clinic for further diagnostic testing. Consistent with data from the BreastCheck screening programme, it was assumed that 75% would have a breast ultrasound; 32% would have additional mammographic imaging, and 35% would undergo biopsy of the suspect lesion(s). The unit cost of ultrasound and biopsy were obtained from the finance departments of regional cancer centres. The cost of repeat mammographic imaging was assumed to be the same as for a surveillance mammogram. In the absence of available Irish cost data, costs for histopathology and receptor testing (ER, PR and HER2) of biopsied lesions were obtained from the UK NHS and transferred to euro using Purchasing Power Parity. Following a confirmed diagnosis of breast cancer, it was assumed that 10%-15% of women would undergo an MRI for staging purposes or to rule out breast cancer in the contralateral breast irrespective of the imaging used in surveillance. It

is probable that in reality a pre-operative MRI is less likely where the surveillance imaging is MRI and more likely where the surveillance imaging is digital mammography. The unit cost for an MRI was applied.

Radiotherapy

Radiotherapy is administered post-operatively to patients with DCIS and stages I-IV breast cancer as primary locoregional treatment. Based on NCRI data and a number of regional cancer centres, it was assumed that 40% of patients with DCIS would receive whole breast radiotherapy. For those with stages I to IV disease it was assumed that 74%, 74%, 79% and 35%, respectively would receive radiotherapy to the whole breast and to the chest well and regional lymph nodes if indicated. Based on international clinical guidelines and expert opinion, radiotherapy was assumed to comprise 45 – 50Gy in 25 fractions over five weeks. The unit cost of radiotherapy was estimated from DRG costs (R64 outpatient radiotherapy) which gave a base-case estimate of €6,310.

Endocrine therapy

Adjuvant endocrine therapy is indicated for women with breast cancer that is oestrogen receptor (ER) or progesterone receptor (PR) positive. Based on data from the NCRI, a regional cancer centre and expert opinion, it was assumed that 20% of women with DCIS and 80%, 75%, 75% and 75% of those with stages I to IV disease, respectively would receive endocrine therapy. The cost of endocrine treatment was specific to whether the patient was pre- or post-menopausal. It was assumed that 0% of women were menopausal prior to age 40, 7% in the 40-44 year age band, 34% in the 45-49 year age band, 77% in the 50-54 year age band, and 100% thereafter. Based on international clinical guidelines and expert opinion, all pre-menopausal women were assumed to receive tamoxifen 20mg orally per day for five years. Women who are post-menopausal are prescribed an aromatase inhibitor (either anastrazole 1mg or letrozole 2.5mg orally per day) for five years. The cost of these medications was obtained from the HSE's Primary Community Care Service (PCRS) and adjusted to reflect the cost to the HSE in line with current guidelines. It was assumed that 50% of those prescribed an aromatase inhibitor would receive anastrazole and 50% letrozole. The five-year base-case cost estimate of adjuvant endocrine therapy is €618 for pre-menopausal and €5,504 for post-menopausal women. Costs were varied +/-20% around these values (that is, €494-€742 and €4,403-€6,605, respectively). Taking into account the age distribution of patients and the proportion patients likely to be menopausal at those ages, a weighted average cost of €1,820 was used in the analysis.

Surgery

Surgery is indicated as primary therapy for local disease in women with DCIS and stage I to IV disease. Surgery may comprise mastectomy, wide local excision, axillary clearance and sentinel lymph node biopsy and resection depending on the stage of the disease. The proportion of women receiving the specific types of surgery is outlined in Chapter 5, Table 5.4; again, this breakdown was informed by data from the NCRI, HIPE, regional cancer centres and expert opinion. The cost of surgery was estimated using weighted average DRG costs. Cost data for each of the surgical procedures were generated based on weighted DRGs obtained from the 2011 HIPE data for women less than 50 years with primary diagnosis codes of C50 and D05 (Table App 3.2).

Table App 3.2 Weightings for different DRGs for surgical procedures

Procedure	DRG	Cost weight	
		Inpatient	Day case
Mastectomy	J01B	0.01	0.00
	J06Z	0.80	0.01
	J14Z	0.18	0.00
Wide local excision	J06Z	0.44	0.21
	J07Z	0.09	0.25
	J11Z	0.00	0.00
	J14Z	0.01	0.00
Axillary clearance	J06Z	0.34	0.07
	J07Z	0.01	0.18
	Q02B	0.01	0.02
	R02B	0.01	0.00
	R02C	0.22	0.02
	R04B	0.01	0.09
	T01B	0.00	0.01
Sentinel node biopsy	J06Z	0.14	0.51
	Q02B	0.04	0.04
	R02B	0.03	0.01
	R02C	0.05	0.17

Chemotherapy costs

Chemotherapy is indicated as systemic adjuvant therapy in women with invasive breast cancer. Adjuvant therapy may also comprise use of a biological agent (e.g., trastuzumab, lapatanib) for women with HER2+ve disease. Table 5.4 in Chapter 5

summarises the weighted average cost of chemotherapy and biological agents for women undergoing chemotherapy. Details of how these costs were derived for each regimen are provided below.

Costs were based on protocols used in two regional cancer centres as notified by medical oncologists specialising in the treatment of breast cancer. Costs comprise the drug component costs (excluding VAT), the cost of aseptic compounding, administration time, monitoring costs and the cost of ancillary medications. Drug acquisition costs were based on a woman with a body surface area of 1.70m^2 (median weight 64Kg, median height 1.63m for a woman under 50 years), with allowance for vial wastage. The cost of intravenous chemotherapy was based on average purchase costs reported by a number of regional cancer centres. Costs of oral chemotherapy agents, ancillary medicines (neutrophil support, anti-emetics) were obtained from the HSE's Primary Community Care Service (PCRS) and adjusted to reflect the cost to the HSE in line with current guidelines. Staff costs for nursing, pharmacy and clinical staff were estimated from 2010 Department of Health consolidated pay scales and, adjusted for pay-related costs and calculated pro-rata in accordance with current guidelines for economic evaluation.

Based on clinician feedback, the choice of chemotherapy regimen used depends on the tumour characteristics (Herceptin receptor 2 (HER2) positive or negative, or so called 'triple negative' – negative for progesterone, oestrogen and HER2 receptors), the pathological stage (stage IV metastatic breast cancer; or node negative or node positive if stage I, II or III;) and their risk of relapse, low risk (pre-menopausal, node–ve or post-menopausal with < 4 affected nodes) or high risk (pre-menopausal node+ve or post-menopausal with ≥4 nodes positive). Based on data from the NCRI, 6% were assumed to have presented with metastatic disease.

Information on chemotherapy protocols in use for each of the above categories was supplied by medical oncologists from two regional cancer centres. The regimens used and their estimated costs are outlined in Table App 3.3.

Table App 3.3 Description of first-line chemotherapy protocols and their average cost per course

Agents, Dose and Day	Frequency	Number of Cycles	Av Cost of Course*
Docetaxel 75 mg/m^{2}IVI Day 1	Every 21 days	4	€7,499
Cyclophosphamide 600 mg/m^2 IVP Day 1	Every 21 days	4	
Doxorubicin 60 mg/m^2 IVP Day 1	Every 14 day	4	€14,099
Cyclophosphamide 600mg/m^2 IVP Day 1	Every 14 day	4	
Followed by			
Paclitaxel 175mg/m^2 IVI Day 1	Every 14 days	4	
Doxorubicin 60mg/m^2 IVP Day 1	Every 14 days	4	€43,121
Cyclophosphamide 600mg/m^2 IVP Day 1	Every 14 days	4	
Followed by			
Paclitaxel 80mg/m^2 IVI Day 1	Every 7 days	12	
Trastuzumab 2mg/m^2 IVI**	Every 7 days	12	
Followed by:			
Trastuzumab 6mg/m^2 IVI**	Every 21 days	To complete 52 wks Tx	
Docetaxel 75mg/m^2 IVI Day 1	Every 21 days	6	€48,343
Carboplatin AUC 6 IVI Day 1	Every 21 days	6	
Trastuzumab 2mg/m^2 IVI**	Every 21 days	6	
Followed by:			
Trastuzumab 6mg/m^2 IVI**	Every 21 days	To complete 52 wks Tx	
Doxorubicin 60mg/m^2 IVP Day 1	Every 21 days	4	€8,894
Cyclophosphamide 600mg/m^2 IVP Day 1	Every 21 days	4	
Followed by			
Docetaxel 75mg/m^2 IVI day 1	Every 21 days	4	
Doxorubicin 60mg/m^2 IVP Day 1	Every 21 days	4	€53,486
Cyclophosphamide 600mg/m^2 IVP Day 1	Every 21 days	4	
Followed by			
Docetaxel 100mg/m^2 IVI day 1	Every 21 days	4	
Trastuzumab 2mg/m^2 IVI**	Every 7 days	12	
Followed by:			
Trastuzumab 6mg/m^2 IVI**	Every 21 days	To complete 52 wks Tx	

* Average cost of therapy comprises ingredient costs, costs of aseptic compounding, cost of administration and routine monitoring and the cost of all ancillary medications including neutrophil support. Costs derived from an average reported by a number of regional cancer centres.

** Trastuzumab given as a loading dose of 4mg/m^2 for the first dose.

Abbreviations: IVI, intravenous infusion; IVP, intravenous push; TX, treatment.

Although up to 20% of women presenting with stage IV may achieve a complete remission, there is limited data to support the duration of remission achieved. As reported in Tables 2.1 and 5.4 (Chapters 2 and 5), only 6% of women aged less than

50 years that are diagnosed with breast cancer present with stage IV disease; five-year mortality for this cohort exceeds 0.574. The majority of patients who have relapsed metastatic breast cancer do not achieve complete remission. Expert advice was that the current practice is to use continuous chemotherapy in patients with less than complete remission, as respite periods are invariably short. There may, however, be short intervals of one to two weeks between courses while re-evaluation of disease is undertaken. It was therefore assumed that the active treatment phase comprised use of consecutive chemotherapy regimens (first line, second line etc.) with regimen changes coinciding with average time to disease progression as reported in the relevant randomised clinical trial supporting the use of that regimen. Table App 3.4 lists representative first, second and third line regimens for metastatic breast cancer.

Table App 3.4 Description of chemotherapy protocols routinely used in metastatic breast cancer and their average cost per course

Agents, Dose and Day	Frequency	Number of Cycles*	Av Cost of Course**
Paclitaxel 80 mg/m^{2}IVI Day 1	Every 7 days	37	€24,720
Doxorubicin 60 mg/m^2 IVP Day 1	Every 14 days	4	€14,099
Cyclophosphamide 600mg/m^2 IVP Day 1	Every 14 days	4	
Followed by			
Paclitaxel 175mg/m^2 IVI day 1	Every 14 days	4	
Paclitaxel 80mg/m^2 IVI day 1	Every 7 days	37	€47,379
Trastuzumab 2mg/m^2 IVI***	Every 7 days	37	
Capecitabine 1000-1250mg/m^2 po bid Days 1-14	Every 21 days	6	€3,206
Capecitabine 1000-1250 mg/m^2 po bid Days 1-14	Every 21 days	12	€28,605
Lapatinib 1250 mg po qd Days 1-21		12	
Vinorelbine 30mg/m^2 Day 1 and Day 8	Every 21 days	9	€17,409
Vinorelbine 30mg/m^2 Day 1 and Day 8	Every 21 days	9	€32,218
Trastuzumab 6mg/m^2 IVI***	Every 21 days	9	

* Based on the time to disease progression in RCT.

** Average cost of therapy comprises ingredient costs, costs of aseptic compounding, cost of administration and routine monitoring and the cost of all ancillary medications including neutrophil support.

*** Trastuzumab given as a loading dose of 4mg/m^2 for the first dose.

Using this data, the estimated weighted average cost of treating breast cancer was €17,415. This estimate includes the cost of the chemotherapy, biological agents, ancillary medications, aseptic compounding, administration and monitoring costs.

Routine monitoring costs (e.g. laboratory tests, imaging) that a patient would receive while undergoing chemotherapy were also included in the cost estimates. Monitoring

comprised blood work (full blood count and biochemistry) prior to the administration of chemotherapy and an evaluation of cardiac ejection fraction (Muga scan at baseline and every three months thereafter) for patients receiving Trastuzumab. Patients with stage IV breast cancer (as relapse or presenting de novo with metastatic disease) are scanned at baseline, at three-monthly intervals and, or at disease progression using CT scan of the chest /abdomen/pelvis, chest X-ray and bone scan as appropriate. The unit cost of this imaging and blood work was obtained from Casemix data supplied by the finance departments of regional cancer centres.

Appendix 4 - Economic evaluation results

The economic models presented in Chapter 5 include the point estimates for the main outcomes of interest. In this Appendix, further detail is provided on the results.

App 4.1 BRCA1 subgroup

The 19 strategies modelled for the subgroup of women with *BRCA1* mutations are shown in Table App 4.1 below.

Table App 4.1 Surveillance strategies modelled for *BRCA1* subgroup

Strategy	20-24	25-29	30-34	35-39	40-49
A01	No screen	No screen	No screen	No screen	No screen
A02	No screen	No screen	No screen	No screen	MRI (24)
A03	No screen	No screen	No screen	No screen	MRI (12)
A04	No screen	No screen	No screen	No screen	DMX+MRI (12)
A05	No screen	No screen	No screen	MRI (24)	MRI (12)
A06	No screen	No screen	No screen	MRI (12)	MRI (12)
A07	No screen	No screen	No screen	MRI (12)	DMX+MRI (12)
A08	No screen	No screen	No screen	DMX+MRI (12)	DMX+MRI (12)
A09	No screen	No screen	MRI (24)	MRI (12)	MRI (12)
A10	No screen	No screen	MRI (24)	MRI (12)	DMX+MRI (12)
A11	No screen	No screen	MRI (24)	DMX+MRI (12)	DMX+MRI (12)
A12	No screen	No screen	MRI (12)	MRI (12)	MRI (12)
A13	No screen	No screen	MRI (12)	MRI (12)	DMX+MRI (12)
A14	No screen	No screen	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
A15	No screen	No screen	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)
A16	No screen	MRI (24)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
A17	No screen	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
A18	No screen	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)
A19	No screen	MRI (12)	MRI (12)	MRI (12)	MRI (12)

Table App 4.2 ICERs for surveillance strategies on the frontier for the *BRCA1* subgroup

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER
A01	19.7188	5,548	-	-	-
A02 vs. A01	19.7544	6,419	0.0356	871	24,441
A03 vs. A02	19.7742	7,133	0.0198	714	36,034
A05 vs. A03	19.7845	7,794	0.0103	661	64,006
A06 vs. A05	19.7904	8,182	0.0059	388	66,265
A19 vs. A06	19.8150	10,763	0.0246	2582	104,870

Note: ICER – incremental cost-effectiveness ratio.

Table App 4.3 Cost-effectiveness results for surveillance strategies for women with *BRCA1* mutations

Strategy	QALYs per person			Cost per person			ICER[1]			Mortality per 1,000[2]			Probability effective[3]	Probability on frontier[4]
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI		
A1	19.7188	19.5755	19.8526	5,548	5,020	6,095	-	-	-	46	33	59	-	-
Incremental relative to no surveillance														
A2	0.0344	0.0074	0.0686	868	721	1,047	25,370	12,088	120,683	-6	-1	-11	0.99	0.65
A3	0.0544	0.0209	0.0937	1,582	1,390	1,810	29,244	16,588	78,087	-8	-3	-15	1.00	0.57
A4	0.0537	0.0183	0.0948	2,184	1,976	2,427	40,815	22,498	121,272	-9	-3	-15	1.00	0.07
A5	0.0647	0.0259	0.1102	2,249	2,013	2,518	34,804	19,969	88,986	-10	-4	-17	1.00	0.34
A6	0.0700	0.0297	0.1179	2,635	2,379	2,926	37,464	21,778	90,519	-11	-4	-18	1.00	0.29
A7	0.0694	0.0268	0.1187	3,239	2,973	3,549	46,742	26,684	123,736	-11	-5	-19	1.00	0.07
A8	0.0658	0.0208	0.1165	3,668	3,390	3,990	55,756	30,844	180,029	-11	-4	-19	1.00	0.02
A9	0.0780	0.0308	0.1314	3,381	3,089	3,694	43,463	25,241	112,411	-12	-5	-20	1.00	0.27
A10	0.0768	0.0290	0.1326	3,985	3,687	4,305	51,773	29,513	141,953	-12	-5	-20	1.00	0.07
A11	0.0732	0.0225	0.1298	4,416	4,101	4,750	60,258	33,415	201,077	-12	-5	-20	1.00	0.02
A12	0.0820	0.0333	0.1375	3,843	3,545	4,171	46,992	27,398	117,355	-12	-5	-20	1.00	0.18
A13	0.0808	0.0313	0.1383	4,447	4,140	4,785	55,277	31,534	145,148	-13	-5	-21	1.00	0.05
A14	0.0767	0.0249	0.1364	4,879	4,559	5,231	63,581	35,178	200,227	-12	-5	-20	1.00	0.01
A15	0.0700	0.0149	0.1307	5,418	5,084	5,784	77,486	40,691	368,460	-12	-4	-20	1.00	0.02
A16	0.0865	0.0299	0.1515	5,720	5,387	6,102	66,199	37,263	192,371	-13	-6	-22	1.00	0.07
A17	0.0917	0.0328	0.1589	6,254	5,902	6,643	68,330	38,908	197,048	-14	-6	-22	1.00	0.05
A18	0.0956	0.0401	0.1619	5,823	5,482	6,194	60,850	35,481	147,093	-14	-6	-22	1.00	0.25
A19	0.0969	0.0426	0.1608	5,217	4,884	5,579	53,648	32,019	125,882	-13	-6	-22	1.00	0.57

1. *ICERs relative to no surveillance. These differ from those presented in main analysis as they are computed for each simulated cohort, rather than using the median costs and benefits computed across simulations.*
2. *Negative mortality figures indicate a reduction in mortality relative to no surveillance.*
3. *Probability effective is the probability that a strategy will result in a QALY gain relative to no surveillance.*
4. *Probability on frontier is the probability that a strategy appears on the cost-effectiveness frontier.*

Table App 4.4 Budget impact analysis results for surveillance strategies for women with *BRCA1* mutations

Strategy	Budget impact			False positives			Digital mammograms			MRIs			Further tests			MR-guided biopsies		
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI
A1	219,806	63,321	460,817	0	0	0	0	0	0	3	0	8	12	4	21	0	0	1
Incremental relative to no surveillance																		
A2	36,255	8,818	116,359	5	1	11	0	0	0	61	31	98	6	1	13	2	0	6
A3	74,774	22,627	179,831	10	4	20	0	0	0	128	66	200	12	4	22	4	1	10
A4	96,324	32,702	207,669	15	6	27	124	64	193	129	67	202	17	7	30	6	1	12
A5	84,971	26,966	195,288	12	4	22	0	0	0	146	76	227	14	5	25	5	1	11
A6	91,791	30,528	209,843	13	5	24	0	0	0	159	83	245	15	6	27	5	1	12
A7	113,103	40,956	238,939	18	7	31	124	64	193	160	84	247	20	8	35	7	2	14
A8	118,016	43,660	245,535	19	8	33	154	81	238	161	84	247	21	9	37	7	2	15
A9	96,794	32,790	215,902	14	5	25	0	0	0	169	89	259	16	6	29	6	1	12
A10	118,402	43,701	244,294	19	8	33	124	64	193	171	90	261	21	9	36	7	2	15
A11	122,921	46,872	251,096	20	9	34	154	81	238	171	90	262	22	10	38	8	2	15
A12	99,849	34,131	221,757	15	5	26	0	0	0	176	92	269	17	7	30	6	1	12
A13	121,250	45,882	251,619	19	8	34	124	64	193	177	93	270	22	9	37	7	2	15
A14	125,879	48,442	258,875	21	9	35	154	81	238	178	93	271	23	10	39	8	2	16
A15	128,546	50,076	262,683	21	9	36	171	90	260	178	93	271	24	10	40	8	2	16
A16	127,632	49,551	260,938	21	9	36	154	81	238	182	95	277	23	10	40	8	2	16
A17	128,746	50,021	262,427	21	9	36	154	81	238	185	97	281	24	10	40	8	2	16
A18	124,371	47,340	255,973	20	8	34	124	64	193	185	97	281	22	9	38	8	2	15
A19	103,019	35,710	226,626	15	6	27	0	0	0	183	96	279	17	7	31	6	1	13

App 4.2 *BRCA2* subgroup

The 19 strategies modelled for the subgroup of women with *BRCA2* mutations are shown in Table App 4.5 below.

Table App 4.5 Surveillance strategies modelled for *BRCA2* subgroup

Strategy	20-24	25-29	30-34	35-39	40-49
B01	No screen	No screen	No screen	No screen	No screen
B02	No screen	No screen	No screen	No screen	MRI (24)
B03	No screen	No screen	No screen	No screen	MRI (12)
B04	No screen	No screen	No screen	No screen	DMX+MRI (12)
B05	No screen	No screen	No screen	MRI (24)	MRI (12)
B06	No screen	No screen	No screen	MRI (12)	MRI (12)
B07	No screen	No screen	No screen	MRI (12)	DMX+MRI (12)
B08	No screen	No screen	No screen	DMX+MRI (12)	DMX+MRI (12)
B09	No screen	No screen	MRI (24)	MRI (12)	MRI (12)
B10	No screen	No screen	MRI (24)	MRI (12)	DMX+MRI (12)
B11	No screen	No screen	MRI (24)	DMX+MRI (12)	DMX+MRI (12)
B12	No screen	No screen	MRI (12)	MRI (12)	MRI (12)
B13	No screen	No screen	MRI (12)	MRI (12)	DMX+MRI (12)
B14	No screen	No screen	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
B15	No screen	No screen	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)
B16	No screen	MRI (24)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
B17	No screen	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
B18	No screen	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)
B19	No screen	MRI (12)	MRI (12)	MRI (12)	MRI (12)

Table App 4.6 ICERs for surveillance strategies on the frontier for the *BRCA2* subgroup

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER
B01	19.8633	4,199	-	-	-
B02 vs. B01	19.8880	5,016	0.0247	817	33,079
B03 vs. B02	19.9021	5,707	0.0141	691	49,036
B05 vs. B03	19.9086	6,330	0.0065	623	95,548
B09 vs. B05	19.9192	7,410	0.0106	1080	102,045
B19 vs. B19	19.9330	9,203	0.0138	1793	129,846

Note: ICERs – incremental cost-effectiveness ratio.

Table App 4.7 Cost-effectiveness results for surveillance strategies for women with *BRCA2* mutations

Strategy	QALYs per person			Cost per person			ICER[1]			Mortality per 1,000[2]			Probability effective[3]	Probability on frontier[4]
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI		
B1	19.8633	19.7341	19.9871	4,199	3,742	4,665	-	-	-	33	22	44	-	-
Incremental relative to no surveillance														
B2	0.0230	0.0013	0.0510	812	697	973	35,593	15,108	630,663	-4	0	-8	0.98	0.62
B3	0.0370	0.0099	0.0694	1,504	1,345	1,698	40,830	21,121	150,516	-6	-1	-11	1.00	0.53
B4	0.0355	0.0055	0.0704	2,098	1,925	2,306	59,258	29,235	378,248	-6	-1	-11	0.99	0.07
B5	0.0429	0.0112	0.0795	2,128	1,941	2,359	49,872	26,248	191,199	-7	-2	-12	1.00	0.26
B6	0.0466	0.0127	0.0857	2,504	2,303	2,747	53,752	29,040	197,551	-7	-2	-13	1.00	0.19
B7	0.0452	0.0094	0.0861	3,097	2,888	3,348	68,401	35,562	335,396	-7	-2	-13	0.99	0.05
B8	0.0421	0.0052	0.0847	3,506	3,282	3,761	83,281	40,620	687,675	-7	-2	-14	0.99	0.02
B9	0.0536	0.0150	0.0984	3,212	2,985	3,483	60,035	32,091	218,095	-8	-2	-14	1.00	0.26
B10	0.0519	0.0118	0.0987	3,806	3,571	4,081	73,121	37,848	328,246	-8	-2	-15	0.99	0.06
B11	0.0486	0.0068	0.0974	4,216	3,972	4,494	86,898	42,808	615,592	-8	-2	-15	0.99	0.02
B12	0.0565	0.0178	0.1034	3,661	3,422	3,939	64,875	34,751	208,443	-8	-3	-15	1.00	0.15
B13	0.0548	0.0144	0.1040	4,256	4,006	4,539	77,510	40,611	298,700	-8	-3	-15	1.00	0.04
B14	0.0517	0.0088	0.1016	4,665	4,407	4,953	90,351	45,350	541,606	-8	-2	-15	0.99	0.01
B15	0.0478	0.0020	0.0996	5,172	4,906	5,472	108,245	51,277	2,684,141	-8	-2	-15	0.98	0.04
B16	0.0604	0.0133	0.1146	5,482	5,213	5,800	90,719	46,945	414,781	-9	-3	-16	0.99	0.08
B17	0.0638	0.0157	0.1197	6,013	5,734	6,327	94,160	49,581	383,626	-9	-3	-16	1.00	0.03
B18	0.0673	0.0204	0.1222	5,602	5,336	5,911	83,145	45,148	275,151	-10	-3	-17	1.00	0.20
B19	0.0688	0.0232	0.1230	5,005	4,749	5,319	72,868	40,468	217,722	-9	-3	-16	1.00	0.53

1. *ICERs relative to no surveillance. These differ from those presented in main analysis as they are computed for each simulated cohort, rather than using the median costs and benefits computed across simulations.*
2. *Negative mortality figures indicate a reduction in mortality relative to no surveillance.*
3. *Probability effective is the probability that a strategy will result in a QALY gain relative to no surveillance.*
4. *Probability on frontier is the probability that a strategy appears on the cost-effectiveness frontier.*

Table App 4.8 Budget impact analysis results for surveillance strategies for women with *BRCA2* mutations

Strategy	Budget impact			False positives			Digital mammograms			MRIs			Further tests			MR-guided biopsies		
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI
B1	126,603	14,859	326,298	0	0	0	0	0	0	2	0	6	7	2	15	0	0	1
Incremental relative to no surveillance																		
B2	22,651	5,578	85,011	4	0	9	0	0	0	44	18	80	4	1	10	1	0	5
B3	47,977	13,239	128,995	8	2	16	0	0	0	93	40	162	9	2	19	3	0	8
B4	63,337	19,490	151,818	11	3	23	90	38	157	94	40	164	12	4	25	4	0	10
B5	54,376	15,949	142,336	9	2	18	0	0	0	106	46	185	10	3	20	3	0	9
B6	58,909	16,841	155,476	10	3	20	0	0	0	115	50	200	11	3	22	4	0	9
B7	74,150	23,622	175,582	13	4	26	90	38	157	116	50	202	14	4	28	5	1	11
B8	77,410	25,062	181,635	14	4	27	112	49	194	116	51	202	15	5	30	5	1	12
B9	62,559	18,268	160,851	10	3	21	0	0	0	123	54	212	11	3	23	4	0	9
B10	77,483	25,055	181,115	14	4	27	90	38	157	124	54	215	15	5	29	5	1	12
B11	80,758	26,397	186,688	15	5	28	112	49	194	124	55	215	16	5	31	5	1	12
B12	64,634	19,029	166,078	11	3	22	0	0	0	127	56	221	12	3	24	4	0	10
B13	79,599	25,986	187,558	14	4	28	90	38	157	128	56	222	16	5	30	5	1	12
B14	82,964	27,471	191,515	15	5	29	112	49	194	128	56	223	17	5	31	5	1	12
B15	84,815	28,325	193,629	16	5	30	123	54	214	129	56	224	17	6	32	5	1	12
B16	84,334	28,036	193,844	15	5	30	112	49	194	132	58	228	17	6	32	5	1	12
B17	85,184	28,339	193,868	16	5	30	112	49	194	134	59	231	17	6	32	5	1	12
B18	81,672	27,054	191,169	15	5	28	90	38	157	133	59	231	16	5	31	5	1	12
B19	66,781	20,360	167,434	11	3	22	0	0	0	132	58	229	12	4	25	4	0	10

App 4.3 Other high penetrance genetic mutations subgroup

The 10 strategies modelled for the subgroup of women with other high penetrance genetic mutations are shown in Table App 4.9 below.

Table App 4.9 Surveillance strategies modelled for subgroup with other high penetrance genetic mutations

Strategy	20-24	25-29	30-34	35-39	40-49
C01	No screen	No screen	No screen	No screen	No screen
C02	MRI (6)	MRI (6)	MRI (6)	MRI (6)	MRI (6)
C03	MRI (12)	MRI (12)	MRI (12)	MRI (12)	MRI (12)
C04	MRI (12)	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)
C05	MRI (12)	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
C06	MRI (12)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)
C07	MRI (6)	MRI (6)	MRI (12)	MRI (12)	MRI (12)
C08	MRI (6)	MRI (6)	MRI (12)	MRI (12)	DMX+MRI (12)
C09	MRI (6)	MRI (6)	MRI (12)	DMX+MRI (12)	DMX+MRI (12)
C10	MRI (6)	MRI (6)	DMX+MRI (12)	DMX+MRI (12)	DMX+MRI (12)

Table App 4.10 ICERs for surveillance strategies for other high penetrance mutation carriers

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER
C01	19.4767	5,912	-	-	-
C03 vs. C01	19.6757	12,986	0.1990	7074	35,542
C07 vs. C03	19.7337	15,915	0.0579	2929	50,562
C02 vs. C07	19.7485	19,119	0.0148	3204	216,168

Note: ICER – incremental cost-effectiveness ratio.

Table App 4.11 Cost-effectiveness results for surveillance strategies for women with other high penetrance genetic mutations

Strategy	QALYs per person			Cost per person			ICER[1]			Mortality per 1,000[2]			Probability effective[3]	Probability on frontier[4]
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI		
C1	19.4767	19.2707	19.6637	5,912	5,232	6,626	-	-	-	61	47	76	-	-
Incremental relative to no surveillance														
C2	0.2707	0.1546	0.3988	13,206	12,642	13,834	48,730	32,746	85,572	-23	-14	-34	1.00	0.86
C3	0.1965	0.0966	0.3093	7,066	6,581	7,618	35,985	22,406	74,658	-17	-9	-27	1.00	0.71
C4	0.1952	0.0952	0.3092	7,613	7,122	8,164	38,937	24,255	81,037	-17	-9	-26	1.00	0.02
C5	0.1931	0.0918	0.3079	7,998	7,501	8,544	41,461	25,683	88,858	-17	-9	-27	1.00	0.01
C6	0.1898	0.0868	0.3046	8,482	7,978	9,031	44,710	27,403	99,069	-17	-8	-26	1.00	0.01
C7	0.2561	0.1423	0.3852	10,005	9,459	10,629	39,040	25,830	70,867	-22	-13	-32	1.00	0.91
C8	0.2547	0.1412	0.3817	10,549	10,008	11,167	41,439	27,303	75,740	-22	-13	-32	1.00	0.08
C9	0.2522	0.1393	0.3797	10,934	10,396	11,555	43,330	28,375	79,461	-22	-12	-32	1.00	0.04
C10	0.2493	0.1342	0.3787	11,422	10,867	12,049	45,845	29,813	84,961	-21	-12	-32	1.00	0.04

1. *ICERs relative to no surveillance. These differ from those presented in main analysis as they are computed for each simulated cohort, rather than using the median costs and benefits computed across simulations.*
2. *Negative mortality figures indicate a reduction in mortality relative to no surveillance.*
3. *Probability effective is the probability that a strategy will result in a QALY gain relative to no surveillance.*
4. *Probability on frontier is the probability that a strategy appears on the cost-effectiveness frontier.*

Table App 4.12 Budget impact analysis results for surveillance strategies for women with other high penetrance genetic mutations

Strategy	Budget impact			False positives			Digital mammograms			MRIs			Further tests			MR-guided biopsies		
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI
C1	48,970	0	166,918	0	0	0	0	0	0	1	0	3	3	0	7	0	0	0
Incremental relative to no surveillance																		
C2	81,023	47,281	174,589	16	8	26	0	0	0	189	139	244	17	9	27	5	1	11
C3	38,907	21,574	102,749	8	3	14	0	0	0	92	66	123	8	3	15	3	0	7
C4	48,779	28,224	114,817	10	4	18	62	42	86	93	66	124	11	5	19	3	0	8
C5	51,174	29,945	117,460	11	5	19	78	54	105	93	66	125	12	5	20	4	0	8
C6	52,516	30,709	118,746	11	5	19	86	61	115	93	66	125	12	5	20	4	0	8
C7	41,246	22,356	109,614	8	3	15	0	0	0	97	69	130	9	3	16	3	0	7
C8	51,220	29,136	123,554	11	5	19	62	42	86	98	70	130	11	5	20	3	0	8
C9	53,469	30,840	125,699	11	5	20	78	54	105	98	70	130	12	5	20	4	1	8
C10	54,783	31,526	126,975	12	5	20	86	61	115	98	70	130	12	5	21	4	1	9

App 4.4 High familial risk with no identified genetic mutations subgroup

The 11 strategies modelled for the subgroup of women at high familial risk with no identified genetic mutations are shown in Table App 4.13 below.

Table App 4.13 Surveillance strategies modelled for women at high familial risk with no identified genetic mutations

Strategy	20-24	25-29	30-34	35-39	40-49
D01	No screen	No screen	No screen	No screen	No screen
D02	No screen	No screen	No screen	No screen	MRI (12)
D03	No screen	No screen	No screen	No screen	MRI (24)
D04	No screen	No screen	No screen	No screen	DMX (12)
D05	No screen	No screen	No screen	No screen	DMX (24)
D06	No screen	No screen	No screen	No screen	DMX+MRI (12)
D07	No screen	No screen	No screen	No screen	DMX+MRI (24)
D08	No screen	No screen	No screen	DMX (12)	DMX (12)
D09	No screen	No screen	No screen	DMX (24)	DMX (24)
D10	No screen	No screen	DMX (12)	DMX (12)	DMX (12)
D11	No screen	No screen	DMX (24)	DMX (24)	DMX (24)

Table App 4.14 ICERs for surveillance strategies for women with high familial risk but no identified genetic mutations

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER
D01	20.1606	1,242	-	-	-
D03 vs. D01	20.1670	1,956	0.0064	714	111,649
D02 vs. D03	20.1718	2,613	0.0048	657	137,910

Note: ICER – incremental cost-effectiveness ratio.

All strategies modelled had the potential to have less benefit (i.e. reduced QALYs) compared to no surveillance. As a result, the confidence bounds for the ICERs encompass negative ICERs. As the bounds include no effect, this is technically an ICER of infinity (∞) and the bounds for strategy D2, for example, can be written either as (44,924 to -1,276,121) or as (44,924 to ∞; ∞ to -1,276,121).

It can be seen in Table App 4.15 that the mortality difference relative to no surveillance is a mortality reduction or, at worst, no change. However, it can be seen from the confidence bounds that a number of strategies may have higher mortality than no surveillance. Indeed, strategy D10 (annual DMX from age 30) may result in as much as two additional deaths per 1,000 women than no surveillance.

Table App 4.15 Cost-effectiveness results for surveillance strategies for women at high familial risk with no identified genetic mutations

Strategy	QALYs per person			Cost per person			ICER[1]			Mortality per 1,000[2]			Probability effective[3]	Probability on frontier[4]
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI		
D1	20.1606	20.0552	20.2582	1,242	992	1,530	-	-	-	11	5	18	-	-
Incremental relative to no surveillance														
D2	0.0098	-0.0021	0.0299	1,367	1,280	1,478	138,988	44,924	-1,276,121	-2	0	-5	0.90	0.44
D3	0.0053	-0.0045	0.0215	712	646	802	133,576	32,201	-1,351,022	-1	0	-4	0.78	0.28
D4	0.0030	-0.0087	0.0180	554	486	656	188,479	29,585	-1,065,500	-1	1	-3	0.64	0.11
D5	0.0008	-0.0078	0.0140	288	234	372	375,754	19,195	-1,223,755	0	1	-3	0.53	0.26
D6	0.0082	-0.0069	0.0290	1,923	1,827	2,042	237,363	65,372	-2,025,645	-2	0	-5	0.83	0.09
D7	0.0046	-0.0069	0.0221	997	925	1,100	216,761	44,738	-1,417,621	-1	1	-4	0.74	0.05
D8	0.0021	-0.0128	0.0208	937	843	1,068	451,162	43,964	-1,545,372	-1	1	-4	0.59	0.03
D9	0.0016	-0.0113	0.0172	509	437	617	308,210	28,662	-1,112,485	0	1	-3	0.56	0.18
D10[5]	0.0008	-0.0183	0.0249	1,392	1,275	1,549	1,724,976	54,963	-1,901,165	-1	2	-4	0.53	0.07
D11	0.0013	-0.0128	0.0212	712	628	834	529,530	32,259	-1,078,642	-1	1	-3	0.55	0.14

1. *ICERs relative to no surveillance. These differ from those presented in main analysis as they are computed for each simulated cohort, rather than using the median costs and benefits computed across simulations. Negative upper bound implies that the surveillance strategy includes the possibility of lower effect than no surveillance.*
2. *Negative mortality figures indicate a reduction in mortality relative to no surveillance.*
3. *Probability effective is the probability that a strategy will result in a QALY gain relative to no surveillance.*
4. *Probability on frontier is the probability that a strategy appears on the cost-effectiveness frontier.*
5. *The median ACER for strategy D10 (€1,724,976/QALY) is larger than that reported in Table 5.20 (€860,310/QALY). This reflects the different method of computation to facilitate computation of the confidence bounds.*

Table App 4.16 Budget impact analysis results for surveillance strategies for women at high familial risk with no identified genetic mutations

Strategy	Budget impact			False positives			Digital mammograms			MRIs			Further tests			MR-guided biopsies		
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI
D1	763,419	432,563	1,226,334	0	0	0	0	0	0	11	5	19	36	22	55	0	0	1
Incremental relative to no surveillance																		
D2	615,895	418,769	892,697	115	79	167	0	0	0	1,354	998	1,909	124	85	179	39	24	59
D3	324,706	208,507	502,848	56	36	83	0	0	0	652	479	916	62	40	91	20	10	32
D4	243,593	138,486	392,123	58	37	86	1,316	972	1,854	18	9	30	64	41	95	1	0	5
D5	129,017	68,456	234,282	28	16	44	633	465	892	9	4	17	32	19	50	1	0	3
D6	819,468	570,084	1,179,835	168	119	241	1,317	973	1,856	1,370	1,010	1,928	177	125	254	55	35	81
D7	424,282	282,391	635,679	82	55	120	633	465	893	661	484	931	89	60	129	28	16	44
D8	294,508	177,439	465,574	72	47	106	1,629	1,208	2,301	22	12	36	79	52	115	2	0	5
D9	164,220	83,387	288,005	37	23	57	870	640	1,230	12	5	21	43	26	64	1	0	4
D10	320,566	196,531	499,491	80	53	116	1,804	1,333	2,535	25	14	39	86	58	125	2	0	5
D11	163,572	94,384	278,038	39	23	59	867	638	1,219	12	6	22	43	27	65	1	0	4

App 4.5 Moderate risk subgroup

The 11 strategies modelled for the subgroup of women at moderate risk are shown in Table App 4.17 below.

Table App 4.17 Surveillance strategies modelled for women at moderate risk

Strategy	20-24	25-29	30-34	35-39	40-49
E01	No screen	No screen	No screen	No screen	No screen
E02	No screen	No screen	No screen	No screen	MRI (12)
E03	No screen	No screen	No screen	No screen	MRI (24)
E04	No screen	No screen	No screen	No screen	DMX (12)
E05	No screen	No screen	No screen	No screen	DMX (24)
E06	No screen	No screen	No screen	No screen	DMX+MRI (12)
E07	No screen	No screen	No screen	No screen	DMX+MRI (24)
E08	No screen	No screen	No screen	DMX (12)	DMX (12)
E09	No screen	No screen	No screen	DMX (24)	DMX (24)
E10	No screen	No screen	DMX (12)	DMX (12)	DMX (12)
E11	No screen	No screen	DMX (24)	DMX (24)	DMX (24)

Table App 4.18 ICERs for surveillance strategies for women at moderate risk

Strategy	QALYs per person	Cost per person (€)	Incremental QALYs	Incremental cost (€)	ICER
E01	20.2364	470	-	-	-
E03 vs. E01	20.2409	1,160	0.0045	689	153,012
E02 vs. E03	20.2439	1,807	0.0031	647	211,047

Note: ICER – incremental cost-effectiveness ratio.

Table App 4.19 Cost-effectiveness results for surveillance strategies for women at moderate risk

Strategy	QALYs per person			Cost per person			ICER[1]			Mortality per 1,000[2]			Probability effective[3]	Probability on frontier[4]
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI		
E1	20.2364	20.1387	20.3237	470	310	655	-	-	-	5	1	10	-	-
Incremental relative to no surveillance														
E2	0.0072	-0.0012	0.0237	1,332	1,269	1,424	186,315	55,905	-1,967,330	-1	0	-4	0.83	0.33
E3	0.0044	-0.0009	0.0168	686	642	761	156,612	40,579	-2,354,153	-1	0	-3	0.67	0.26
E4	0.0023	-0.0044	0.0152	530	481	612	228,232	35,289	-1,651,100	-1	0	-3	0.59	0.08
E5[5]	-0.0002	-0.0045	0.0111	270	235	334	-108,713	24,507	-2,320,891	0	0	-2	0.42	0.24
E6	0.0065	-0.0034	0.0234	1,878	1,807	1,972	288,296	79,361	-1,705,223	-1	0	-4	0.84	0.08
E7	0.0041	-0.0038	0.0173	966	917	1,043	238,504	56,483	-1,936,002	-1	0	-3	0.68	0.04
E8	0.0038	-0.0062	0.0188	888	820	993	237,761	47,219	-1,378,944	-1	0	-3	0.66	0.05
E9	0.0014	-0.0053	0.0149	476	426	560	349,056	31,935	-1,717,961	0	0	-3	0.52	0.23
E10	0.0026	-0.0104	0.0193	1,318	1,237	1,444	506,792	67,929	-1,351,937	-1	1	-3	0.60	0.02
E11	0.0012	-0.0076	0.0171	670	615	759	544,286	38,296	-1,486,414	0	1	-3	0.52	0.12

1. *ICERs relative to no surveillance. These differ from those presented in main analysis as they are computed for each simulated cohort, rather than using the median costs and benefits computed across simulations. Negative upper bound implies that the surveillance strategy includes the possibility of lower effect than no surveillance.*
2. *Negative mortality figures indicate a reduction in mortality relative to no surveillance.*
3. *Probability effective is the probability that a strategy will result in a QALY gain relative to no surveillance.*
4. *Probability on frontier is the probability that a strategy appears on the cost-effectiveness frontier.*
5. *For strategy E5, the median incremental effect is negative (-0.0002) whereas the difference in median effects as reported in Table 5.23 is positive (0.0015). The confidence bounds for incremental effect encompass the latter figure.*

Table App 4.20 Budget impact analysis results for surveillance strategies for women at moderate risk

Strategy	Budget impact			False positives			Digital mammograms			MRIs			Further tests			MR-guided biopsies		
	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI	Median	LCI	UCI
D1	533,889	259,024	922,776	0	0	0	0	0	0	8	3	15	26	14	43	0	0	2
Incremental relative to no surveillance																		
D2	809,685	541,909	1,222,335	171	114	256	0	0	0	1,990	1,367	2,936	177	118	264	53	32	83
D3	407,967	263,606	632,396	82	52	124	0	0	0	958	658	1,417	86	55	131	27	15	44
D4	304,261	195,774	475,750	86	55	130	1,939	1,334	2,854	25	13	41	90	58	136	1	0	4
D5	156,592	92,179	266,465	42	24	66	932	641	1,375	13	6	23	44	26	70	1	0	3
D6	1,091,287	737,457	1,631,417	249	168	372	1,940	1,335	2,857	2,014	1,387	2,970	255	173	380	76	48	117
D7	546,479	361,158	831,464	121	79	182	932	641	1,375	971	666	1,434	126	82	189	38	22	61
D8	373,250	243,392	578,141	107	70	162	2,405	1,660	3,544	31	17	51	111	73	168	1	0	5
D9	203,048	127,756	335,614	56	34	86	1,283	882	1,893	17	8	29	59	37	91	1	0	4
D10	409,004	265,269	637,644	118	77	179	2,654	1,832	3,910	35	20	56	122	79	184	2	0	5
D11	206,849	126,803	344,545	58	35	89	1,274	880	1,876	17	8	29	60	37	93	1	0	3

References

(1) US National Library of Medicine. *Genetics Home Reference - BRCA1* [Online]. Available from: http://www.ghr.nlm.nih.gov/gene/BRCA1. Accessed on: 2 October 2012.

(2) US National Library of Medicine. *Genetics Home Reference - BRCA2* [Online]. Available from: http://www.ghr.nlm.nih.gov/gene/BRCA2. Accessed on: 2 October 2012.

(3) Expert Advisory Group on Hereditary Cancer Risk. *Framework for the delivery of family risk assessment clinics and associated genetic services for patients at risk of heritable breast cancer*. Dublin: National Cancer Screening Service; 2010.

(4) National Cancer Registry Ireland. *Cancer in Ireland 2011: Annual report of the National Cancer Registry*. Cork, Ireland: National Cancer Registry Ireland; 2011.

(5) Balmaña J, Diez O, Rubio I, Castiglione M, On behalf of the ESMO Guidelines Working Group. BRCA in breast cancer: ESMO Clinical Practice Guidelines. *Annals of Oncology.* 2010; 21(suppl 5) p.v20-v22.

(6) Hill AD, Doyle JM, McDermott EW, O'Higgins NJ. Hereditary breast cancer. *Br J Surg.* 1997; 84(10) pp.1334-9.

(7) National Institute for Health and Clinical Effectiveness. NICE Clinical Guidelines. *Familial breast cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care*. London: NICE; 2006.

(8) Nathanson KL, Wooster R, Weber BL. Breast cancer genetics: what we know and what we need. *Nat Med.* 2001; 7(5) pp.552-6.

(9) Shen Y, Yang Y, Inoue LYT, Munsell MF, Miller AB, Berry DA. Role of Detection Method in Predicting Breast Cancer Survival: Analysis of Randomized Screening Trials. *Journal of the National Cancer Institute.* 2005; 97(16) pp.1195-203.

(10) Berry DA. Benefits and Risks of Screening Mammography for Women in Their Forties: a Statistical Appraisal. *Journal of the National Cancer Institute.* 1998; 90(19) pp.1431-9.

(11) Duffy SW, Sasieni P, Olsen AH, Cafferty FH. Modelling the likely effect of the increase of the upper age limit from 70 to 73 for breast screening in the UK National Programme. *Statistical Methods in Medical Research.* 2010; 19(5) pp.547-55.

(12) Lord SJ, Lei W, Craft P, Cawson JN, Morris I, Walleser S, et al. *A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer*. European Journal of Cancer 43[13], pp.1905-17. 2007.

(13) Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Annals of Internal Medicine.* 2010; 152(7) pp.444-55.

(14) Allred DC. Ductal Carcinoma In Situ: Terminology, Classification, and Natural History. *JNCI Monographs.* 2010; 2010(41) pp.134-8.

(15) Kerlikowske K. Epidemiology of Ductal Carcinoma In Situ. *JNCI Monographs.* 2010; 2010(41) pp.139-41.

(16) National Cancer Screening Service. *BreastCheck Programme Report 2009/10*. Dublin, Ireland: National Cancer Screening Service; 2010.

(17) National Cancer Registry Ireland. *Breast cancer incidence, mortality, treatment and survival in Ireland: 1994-2009*. Cork, Ireland: National Cancer Registry; 2012.

(18) National Cancer Registry Ireland. *Cancer projections 2005-2035*. Cork, Ireland: National Cancer Registry Ireland; 2008.

(19) American Joint Committee on Cancer. *Breast Cancer Staging* [Online]. Available from: http://www.cancerstaging.org/staging/posters/breast24x30.pdf.

(20) Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol.* 2007; 8(9) pp.784-96.

(21) Berrino F, De Angelis R, Sant M, Rosso S, Lasota MB, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. *The Lancet Oncology.* 2007; 8(9) pp.773-83.

(22) McPherson K, Steel CM, Dixon JM. Breast cancer-epidemiology, risk factors, and genetics. *BMJ.* 2000; 321

(23) Xue F, Willett WC, Rosner BA, Hankinson SE, Michels KB. Cigarette smoking and the incidence of breast cancer. *Arch Intern Med.* 2011; 171(2) pp.125-33.

(24) McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. *BMJ.* 2000; 321(7261) pp.624-8.

(25) Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D. Multimodality breast cancer screening in women with a familial or genetic predisposition. *Current Oncology.* 2010; 17(3) pp.28-36.

(26) Bermejo-Pérez MJ, Márquez-Calderón S, Llanos-Méndez A. Cancer surveillance based on imaging techniques in carriers of BRCA1/2 gene mutations: a systematic review. *British Journal of Radiology.* 2008; 81(963) pp.172-9.

(27) Trecate G, Vergnaghi D, Manoukian S, Bergonzi S, Scaperrotta G, Marchesini M, et al. MRI in the early detection of breast cancer in women with high genetic risk. *Tumori.* 2006; 92(6) pp.517-23.

(28) Berg WA. Tailored Supplemental Screening for Breast Cancer: What Now and What Next? *American Journal of Roentgenology.* 2009; 192(2) pp.390-9.

(29) Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003; 72(5) pp.1117-30.

(30) Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer.* 1994; 73(3) pp.643-51.

(31) Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet.* 2001; 358(9291) pp.1389-99.

(32) Carroll PA, Nolan C, Clarke R, Farrell M, Gleeson N, Boyle T, et al. *Surgical management of an Irish cohort of BRCA-mutation carriers*. Breast (Edinburgh, Scotland) 20[5], pp.419-23. 2011.

(33) Kuhl CK, Schmutzler RK, Leutner CC, Kempe A, Wardelmann E, Hocke A, et al. Breast MR Imaging Screening in 192 Women Proved or Suspected to Be Carriers of a Breast Cancer Susceptibility Gene: Preliminary Results1. *Radiology.* 2000; 215(1) pp.267-79.

(34) Kriege M, Brekelmans CT, Boetes C, Rutgers EJ, Oosterwijk JC, Tollenaar RA, et al. MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). *Fam Cancer.* 2001; 1(3-4) pp.163-8.

(35) Nelson HD, Huffman LH, Fu R, Harris EL. Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: U.S. Preventive Services Task Force Recommendations. *Annals of Internal Medicine.* 2005; 143(5) pp.362-79.

(36) Causer PA, Jong RA, Warner E, Hill K, Wong JW, Curpen BN, et al. Breast cancers detected with imaging screening in the BRCA population: emphasis on MR imaging with histopathologic correlation. *Radiographics.* 2007; 27(Suppl. 1) p.S165-S182.

(37) Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. *AJR Am J Roentgenol.* 2004; 183(4) pp.1149-57.

(38) Bluemke DA, Gatsonis CA, Chen MH, DeAngelis GA, DeBruhl N, Harms S, et al. Magnetic resonance imaging of the breast prior to biopsy. *JAMA.* 2004; 292(22) pp.2735-42.

(39) Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. *Radiology.* 2004; 233(3) pp.830-49.

(40) Mann RM, Kuhl CK, Kinkel K, Boetes C. Breast MRI: guidelines from the European Society of Breast Imaging. *Eur Radiol.* 2008; 18(7) pp.1307-18.

(41) NHS Breast Screening Programme. *Screening for breast cancer in high-risk women during pregnancy and lactation*. Sheffield, England: NHS Cancer Screening Programme; 2012.

(42) Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS).[Erratum appears in Lancet. 2005 May 28-Jun 3;365(9474):1848]. *Lancet 365(9473):1769-78.* 2005; p.-27.

(43) Abujudeh HH, Kosaraju VK, Kaewlai R. Acute adverse reactions to gadopentetate dimeglumine and gadobenate dimeglumine: experience with 32,659 injections. *AJR Am J Roentgenol.* 2010; 194(2) pp.430-4.

(44) Destounis S, Newell M, Pinsky R. Breast Imaging and Intervention in the Overweight and Obese Patient. *American Journal of Roentgenology.* 2011; 196(2) pp.296-302.

(45) Perry N, Broeders M, de WC, Tornberg S, Holland R, von KL. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition - summary document. *Ann Oncol.* 2008; 19(4) pp.614-22.

(46) Kriege M, Brekelmans CT, Obdeijn IM, Boetes C, Zonderland HM, Muller SH, et al. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. *Breast Cancer Research & Treatment.* 2006; 100(1) pp.109-19.

(47) Health Information and Quality Authority. *National Quality Assurance Standards for Symptomatic Breast Disease Services*. Dublin: Health Information and Quality Authority; 2007.

(48) National Cancer Screening Service. *The benefits and limits of breast screening*. Dublin: National Cancer Screening Service; 2011.

(49) National Cancer Comprehensive Network. *Breast Cancer Screening and Diagnosis: NCCN Clinical Practice Guidelines in Oncology*. 2011.

(50) NHS Breast Screening Programme. *Technical Guidelines for Magnetic Resonance Imaging for the Surveillance of Women at Higher Risk of Developing Breast Cancer - Appendix 4*. Report No.: 68. 2012.

(51) Ontario Ministry of Health and Long Term Care. *Expansion of the Ontario Breast Screening Program (OBSP) to Include Women Aged 30 to 69 at High Risk for Breast Cancer* [Online]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/bulletins/10000/bul10016.pdf. Accessed on: 26 October 2012.

(52) Alberta Health Services. *Risk reduction and surveillance strategies for individuals at high genetic risk for breast and ovarian cancer*. Clinical Practice Guideline BR-011: 2011.

(53) Horsman D, Wilson BJ, Avard D, Meschino WS, Kim SC, Plante M, et al. Clinical management recommendations for surveillance and risk-reduction strategies for hereditary breast and ovarian cancer among individuals carrying a deleterious BRCA1 or BRCA2 mutation. *J Obstet Gynaecol Can.* 2007; 29(1) pp.45-60.

(54) Daly MB, Axilbund JE, Bryant E, Buys S, Eng C, Friedman S, et al. Genetic/familial high-risk assessment: breast and ovarian. *J Natl Compr Canc Netw.* 2006; 4(2) pp.156-76.

(55) Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. *Draft evidence based series: Magnetic resonance imaging screening of women at high-risk for breast cancer*. Canada: Cancer Care Ontario; 2007.

(56) Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin.* 2007; 57(2) pp.75-89.

(57) Nationaal Borstkanker Overleg Nederland. *Richtlijn Mammacarcinoom*. Amsterdam: NBO; 2008.

(58) Department of Health GoWA. *Breast screening in asymptomatic high risk women* [Online]. Available from:

http://www.imagingpathways.health.wa.gov.au/includes/pdf/screen_highrisk.pdf. Accessed on: 26 October 2012.

(59) Hadden WE. Recommendations for the surveillance of young women at increased risk for breast cancer. *Australas Radiol.* 2007; 51(1) pp.1-11.

(60) Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med.* 2004; 351(5) pp.427-37.

(61) Boetes C, Veltman J. Screening women at increased risk with MRI. *Cancer Imaging.* 2005; 5(Spec No. A) p.S10-S15.

(62) Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA.* 2004; 292(11) pp.1317-25.

(63) Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *Journal of Clinical Oncology.* 2005; 23(33) pp.8469-76.

(64) Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer.* 2005; 103(9) pp.1898-905.

(65) Stoutjesdijk MJ, Boetes C, Jager GJ, Beex L, Bult P, Hendriks JHCL, et al. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. *Journal of the National Cancer Institute 93 (14) (pp 1095-1102).* 2001; p.18.

(66) National Institute for Health and Clinical Effectiveness. *Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (Draft for consultation, January 2013)*. London: NICE; 2013.

(67) Maxwell AJ, Ridley NT, Rubin G, Wallis MG, Gilbert FJ, Michell MJ. The Royal College of Radiologists Breast Group breast imaging classification. *Clin Radiol.* 2009; 64(6) pp.624-7.

(68) Review Manager (RevMan V 5.1). [computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

(69) The Cochrane Collaboration. *Diagnostic Test Accuracy Working Group* [Online]. Available from: http://srdta.cochrane.org/. Accessed on: 30 March 2012.

(70) Sardanelli F, Podo F, Santoro F, Manoukian S, Bergonzi S, Trecate G, et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. *Investigative Radiology.* 2011; 46(2) pp.94-105.

(71) Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer.* 1994; 73(3) pp.643-51.

(72) D'Orsi CJ, Mendelson E, Ikeda DM, et al. *Breast Imaging Reporting and Data System: ACR BI-RADS.* Reston, VA: American College of Radiology; 2003.

(73) Meindl A. Comprehensive analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. *Int J Cancer.* 2002; 97(4) pp.472-80.

(74) Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. Multimodality screening of high-risk women: a prospective cohort study. *Journal of Clinical Oncology.* 2009; 27(36) pp.6124-8.

(75) Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, Konig R, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. *J Clin Oncol.* 2010; 28(9) pp.1450-7.

(76) Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med.* 2005; 353(17) pp.1773-83.

(77) Skaane P, Skjennald A. Screen-film mammography versus full-field digital mammography with soft-copy reading: randomized trial in a population-based screening program - the Oslo II Study. *Radiology.* 2004; 232(1) pp.197-204.

(78) Pisano ED, Hendrick RE, Yaffe MJ, Baum JK, Acharyya S, Cormack JB, et al. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology.* 2008; 246(2) pp.376-83.

(79) Verde PE. Meta-analysis of diagnostic test data: A bivariate Bayesian modeling approach. *Statist Med.* 2010; 29(30) pp.3088-102.

(80) Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH. *Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews*. Journal of clinical epidemiology 58[10], pp.982-90. 2005.

(81) R Development Core Team. *R: A Language and Environment for Statistical Computing*. 2011. Vienna, Austria, R Foundation for Statistical Computing.

(82) Verde PE, Sykosch A. *bamdit: Bayesian Meta-Analysis of diagnostic test data*. 2011.

(83) Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. *JAMA.* 1996; 276(1) pp.33-8.

(84) Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology.* 2002; 225(1) pp.165-75.

(85) Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med.* 2003; 138(3) pp.168-75.

(86) Granader EJ, Dwamena B, Carlos RC. MRI and mammography surveillance of women at increased risk for breast cancer: recommendations using an evidence-based approach. *Acad Radiol.* 2008; 15(12) pp.1590-5.

(87) Morrow M, Waters J, Morris E. MRI for breast cancer screening, diagnosis, and treatment. *Lancet.* 2011; 378(9805) pp.1804-11.

(88) Kerlikowske K. Screening mammography in women less than age 50 years. *Curr Opin Obstet Gynecol.* 2012; 24(1) pp.38-43.

(89) Harris R, Sawaya GF, Moyer VA, Calonge N. Reconsidering the criteria for evaluating proposed screening programs: reflections from 4 current and former members of the U.S. Preventive services task force. *Epidemiol Rev.* 2011; 33(1) pp.20-35.

(90) Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev.* 2011;(1) p.CD001877.

(91) Nelson HD, Tyne K, Naik A, Bougatsos C, Chan B, Nygren P, et al. *Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009.

(92) Belkic KL, Cohen M, Marquez M, Mints M, Wilczek B, Berman AH, et al. Screening of high-risk groups for breast and ovarian cancer in Europe: A focus on the Jewish population. *Oncology Reviews.* 2010; 4(4) pp.233-67.

(93) de Gelder R, Fracheboud J, Heijnsdijk EAM, den Heeten G, Verbeek ALM, Broeders MJM, et al. Digital mammography screening: Weighing reduced mortality against increased overdiagnosis. *Preventive medicine.* 2011; 53(3) pp.134-40.

(94) Ringash J. Preventive health care, 2001 update: screening mammography among women aged 40-49 years at average risk of breast cancer. *CMAJ.* 2001; 164(4) pp.469-76.

(95) Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet.* 2006; 368(9552) pp.2053-60.

(96) The Canadian Task Force on Preventive Health Care. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. *Canadian Medical Association Journal.* 2011; 183(17) pp.1991-2001.

(97) Moss S. Screening women aged 40-49 years. *Preventive medicine.* 2011; 53(3) pp.105-7.

(98) Berg WA. Tailored supplemental screening for breast cancer: what now and what next? *AJR Am J Roentgenol.* 2009; 192(2) pp.390-9.

(99) Warner E, Hill K, Causer P, Plewes D, Jong R, Yaffe M, et al. Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011; 29 pp.1664-9.

(100) Komenaka IK, Ditkoff BA, Joseph KA, Russo D, Gorroochurn P, Ward M, et al. The development of interval breast malignancies in patients with BRCA mutations. *Cancer.* 2004; 100(10) pp.2079-83.

(101) Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, et al. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. *Breast Cancer Res.* 2004; 6(1) p.R8-R17.

(102) Foulkes WD, Chappuis PO, Wong N, Brunet JS, Vesprini D, Rozen F, et al. Primary node negative breast cancer in BRCA1 mutation carriers has a poor outcome. *Ann Oncol.* 2000; 11(3) pp.307-13.

(103) Chereau E, Uzan C, Balleyguier C, Chevalier J, De Paillerets BB, Caron O, et al. Characteristics, treatment, and outcome of breast cancers diagnosed in BRCA1 and BRCA2 gene mutation carriers in intensive screening programs including magnetic resonance imaging. *Clinical Breast Cancer.* 2010; 10(2) pp.113-8.

(104) Marrett LD, De P, Airia P, Dryer D. Cancer in Canada in 2008. *CMAJ.* 2008; 179(11) pp.1163-70.

(105) Moller P, Evans DG, Reis MM, Gregory H, Anderson E, Maehle L, et al. Surveillance for familial breast cancer: Differences in outcome according to BRCA mutation status. *Int J Cancer.* 2007; 121(5) pp.1017-20.

(106) National Cancer Screening Service. *Guidelines for Quality Assurance in Mammography Screening, Third Edition*. Dublin: National Cancer Screening Service; 2008.

(107) Hofvind S, Ponti A, Patnick J, Ascunce N, Njor S, Broeders M, et al. False-positive results in mammographic screening for breast cancer in Europe: a literature review and survey of service screening programmes. *J Med Screen.* 2012; 19 Suppl 1 pp.57-66.

(108) Gur D, Wallace LP, Klym AH, Hardesty LA, Abrams GS, Shah R, et al. Trends in recall, biopsy, and positive biopsy rates for screening mammography in an academic practice. *Radiology.* 2005; 235(2) pp.396-401.

(109) National Cancer Screening Service. *Annual Report 2011-2012*. Dublin: National Cancer Screening Service; 2012.

(110) Bermejo-Perez MJ, Marquez CS, Llanos MA. Cancer surveillance based on imaging techniques in carriers of BRCA1/2 gene mutations: a systematic review. *British Journal of Radiology.* 2008; 81 pp.172-9.

(111) Medical Advisory Secretariat. *Cancer screening with digital mammography for women at average risk for breast cancer, magnetic resonance imaging (MRI) for women at high risk: an evidence-based analysis* [Online]. Available from: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_ breast_cancer_screening_20100316.pdf. Accessed on: 11 June 2012.

(112) Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Nogues C, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ.* 2012; 345 p.e5660.

(113) Lowry KP, Lee JM, Kong CY, McMahon PM, Gilmore ME, Cott Chubiz JE, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: A comparative effectiveness analysis. *Cancer.* 2012; 118(8) pp.2021-30.

(114) Grann VR, Patel PR, Jacobson JS, Warner E, Heitjan DF, shby-Thompson M, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. *Breast Cancer Res Treat.* 2011; 125(3) pp.837-47.

(115) Lee JM, McMahon PM, Kong CY, Kopans DB, Ryan PD, Ozanne EM, et al. Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. *Radiology.* 2010; 254(3) pp.793-800.

(116) Moore SG, Shenoy PJ, Fanucchi L, Tumeh JW, Flowers CR. Cost-effectiveness of MRI compared to mammography for breast cancer screening in a high risk population. *BMC Health Serv Res.* 2009; 9(9) pp.1-8.

(117) Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *J Am Med Assoc.* 2006; 295(20) pp.2374-84.

(118) Taneja C, Edelsberg J, Weycker D, Guo A, Oster G, Weinreb J. Cost Effectiveness of Breast Cancer Screening With Contrast-Enhanced MRI in High-Risk Women. *J Am Coll Radiol.* 2009; 6(3) pp.171-9.

(119) Griebsch I, Brown J, Boggis C, Dixon A, Dixon M, Easton D, et al. Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer. *British Journal of Cancer.* 2006; 95(7) pp.801-10.

(120) Norman RPA, Evans DG, Easton DF, Young KC. The cost-utility of magnetic resonance imaging for breast cancer in BRCA1 mutation carriers aged 30-49. *Eur J Health Econ.* 2007; 8(2) pp.137-44.

(121) Health Information and Quality Authority. *Health Technology Assessment (HTA) of a population-based colorectal cancer screening programme in Ireland*. Dublin, Ireland: Health Information and Quality Authority; 2009.

(122) Health Information and Quality Authority. *The Role of Human Papillomavirus Vaccines in Reducing the Risk of Cervical Cancer in Ireland*. Dublin, Ireland: Health Information and Quality Authority; 2008.

(123) National Centre for Pharmacoeconomics. *Economic Evaluation of a Universal Childhood Pneumococcal Conjugate Vaccination Strategy in Ireland*. Dublin, Ireland: National Centre for Pharmacoeconomics; 2007.

(124) National Centre for Pharmacoeconomics. *Cost-effectiveness of hepatitis B vaccination strategies in the Irish Healthcare System: An economic evaluation*. Dublin, Ireland: National Centre for Pharmacoeconomics; 2007.

(125) Health Information and Quality Authority. *Guidelines for the Economic Evaluation of Health Technologies in Ireland*. Dublin, Ireland: Health Information and Quality Authority; 2010.

(126) O'Rourke N. *Review of Referral Patterns and Triage Processes in Symptomatic Breast Units*. Dublin: National Cancer Control Programme; 2012.

(127) Central Statistics Office. *Irish Life Tables No. 15: 2005-2007*. Ireland: CSO; 2009.

(128) Ballard-Barbash R, Taplin SH, Yankaskas BC, Ernster VL, Rosenberg RD, Carney PA, et al. Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. *American Journal of Roentgenology.* 1997; 169(4) pp.1001-8.

(129) Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD. Radiation Effects on Breast Cancer Risk: A Pooled Analysis of Eight Cohorts. *Radiation Research.* 2002; 158(2) pp.220-35.

(130) Hendrick RE, Pisano ED, Averbukh A, Moran C, Berns EA, Yaffe MJ, et al. Comparison of Acquisition Parameters and Breast Dose in Digital Mammography and Screen-Film Mammography in the American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial. *American Journal of Roentgenology.* 2010; 194(2) pp.362-9.

(131) Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. *Br J Cancer.* 2000; 83(10) pp.1301-8.

(132) Antoniou AC, Cunningham AP, Peto J, Evans DG, Lalloo F, Narod SA, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br J Cancer.* 2008; 98(8) pp.1457-66.

(133) Evans DGR, Moran A, Hartley R, Dawson J, Bulman B, Knox F, et al. Long-term outcomes of breast cancer in women aged 30 years or younger, based on family history, pathology and BRCA1/BRCA2/TP53 status. *Br J Cancer.* 2010; 102(7) pp.1091-8.

(134) Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society (B).* 2011; 73(1) pp.3-36.

(135) Remak E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *Br J Cancer.* 2004; 91(1) pp.77-83.

(136) Schleinitz M, DePalo D, Blume J, Stein M. Can differences in breast cancer utilities explain disparities in breast cancer care? *Journal of General Internal Medicine.* 2006; 21(12) pp.1253-60.

(137) Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. *Lung Cancer.* 2005; 48(2) pp.171-85.

(138) Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al. Factors Associated with Age at Natural Menopause in a Multiethnic Sample of Midlife Women. *American Journal of Epidemiology.* 2001; 153(9) pp.865-74.

(139) Department of Health. *NHS Reference Costs 2011-2012* [Online]. Available from: http://www.dh.gov.uk/health/2012/11/2011-12-reference-costs/. Accessed on: 15 January 2013.

(140) Meiser B, Butow P, Barratt A, Friedlander M, Kirk J, Gaff C, et al. Breast cancer screening uptake in women at increased risk of developing hereditary breast cancer. *Breast Cancer Research & Treatment.* 2000; 59(2) pp.101-11.

(141) Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, Gronwald J, Lynch H, Moller P, et al. International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers. *Int J Cancer.* 2008; 122(9) pp.2017-22.

(142) Central Statistics Office. *Vital Statistics - Fourth Quarter and Yearly Summary 2011*. Dublin: Stationery Office; 2012.

(143) Wilson JMG, Jungner G, . *World Health Organisation (WHO) Principles and practice of screening for disease*. 1968.

(144) Health and Consumer Protection Directorate General. *European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth Edition*. 2006.

(145) Council of the EU. Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC). *Official Journal of the European Union.* 2003; L327 pp.34-8.

(146) Council of Europe Committee of Ministers. *Recommendation No. R (94) 11 to Member States on Screening as a tool of preventitive medicine*. 1994.

(147) European network for Health Technology Assessment (EUnetHTA). *HTA Core Model for screening technologies* [Online]. Available from: http://www.eunethta.eu/outputs/final-hta-core-model-screening-technologies.

(148) National Cancer Screening Service. *Framework for the delivery of family risk assessment clinics and associated genetic services for patients at risk of heritable breast cancer. Report of the Expert Advisory Group on hereditary cancer risk*. Dublin: National Cancer Screening Service; 2010.

(149) Medical Council. *Guide to professional conduct and ethics for registered medical practitioners*. Dublin, Ireland: Medical Council; 2009.

(150) Oireachtas. *Disability Act*. Dublin, Ireland: Office of the Attorney General; 2005.

(151) Warner E, Plewes DB, Shumak RS, Catzavelos GC, Di Prospero LS, Yaffe MJ, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. *J Clin Oncol.* 2001; 19(15) pp.3524-31.

(152) Riedl CC, Ponhold L, Flory D, Weber M, Kroiss R, Wagner T, et al. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at

high risk for breast cancer. *Clinical Cancer Research.* 2007; 13(20) pp.6144-52.

(153) Hagen AI, Kvistad KA, Maehle L, Holmen MM, Aase H, Styr B, et al. Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. *Breast 16(4):367-74.* 2007; 16(4) pp.367-74.

(154) Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D. Multimodality breast cancer screening in women with a familial or genetic predisposition. *Current Oncology.* 2010; 17(3) pp.28-36.

(155) Trecate G, Vergnaghi D, Manoukian S, Bergonzi S, Scaperrotta G, Marchesini M, et al. MRI in the early detection of breast cancer in women with high genetic risk. *Tumori.* 2006; 92(6) pp.517-23.

(156) Bigenwald RZ, Warner E, Gunasekara A, Hill KA, Causer PA, Messner SJ, et al. Is mammography adequate for screening women with inherited BRCA mutations and low breast density? *Cancer Epidemiology, Biomarkers & Prevention.* 2008; 17(3) pp.706-11.

(157) Moore SG, Shenoy PJ, Fanucchi L, Tumeh JW, Flowers CR. Cost-effectiveness of MRI compared to mammography for breast cancer screening in a high risk population. *BMC Health Serv Res.* 2009; 9(9) pp.1-8.

(158) Grann VR, Patel PR, Jacobson JS, Warner E, Heitjan DF, shby-Thompson M, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. *Breast Cancer Res Treat.* 2011; 125(3) pp.837-47.

(159) Mundy L, Merlin T, Hodgkinson B, Parrella A. *MRI screening for breast cancer: screening for breast cancer with MRI in genetically high-risk women. Horizon Scanning Prioritising Summary*. Australia: Adelaide Health Technology Assessment (AHTA); Report No.: 3. 2004.

(160) Dunfield L, Severn M. *Effectiveness of magnetic resonance imaging (MRI) screening for women at high risk of breast cancer*. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health (CADTH); Report No.: Technology Report No 93. 2007.

(161) Davidson E, Hancock S. Technical Briefs. *Surveillance of women at high risk of breast cancer*. Christchurch, New Zealand: New Zealand Health Technology Assessment; 2007.

(162) Cerezo Espinosa de los Monteros JJ, Villegas PR. *Magnetic Resonance imaging for breast cancer diagnostics. Systematic review and economic assessment*. Seville: Andalusian Agency for Health Technology Assessment (AETSA); Report No.: 2006/13. 2008.

(163) Medical Services Advisory Committee. *Breast magnetic resonance imaging (MRI)*. Canberra, Australia: Medical Services Advisory Committee; 2006.

(164) Medical Services Advisory Committee. *Cancer screening with digital mammography for women at average risk of breast cancer or MRI for women at high risk*. Canberra, Australia: Medical Services Advisory Committee; 2007.

(165) Information Services Division. *Radiology Services - Detailed Costs* [Online]. Available from: http://www.isdscotland.scot.nhs.uk/Health-Topics/Finance/Costs/Detailed-Tables/Radiology.asp. Accessed on: 9 August 2012.

(166) Cartwright JL. *Options for provision of MRI surveillance in Wales to women with a family history of breast cancer as recommended in NICE Guidance 41*. Mold, United Kingdom: National Public Health Service for Wales; 2008.

Published by the Health Information and Quality Authority.

For further information please contact:

Health Information and Quality Authority
Dublin Regional Office
George's Court
George's Lane
Smithfield
Dublin 7

Phone: +353 (0) 1 814 7400
URL: www.hiqa.ie