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A HEALTH TECHNOLOGY ASSESSMENT:

Diagnostic accuracy, clinical effectiveness and budget impact of screening BRCA1/2 mutation carriers by MRI

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Key messages

BRCA1 and BRCA2 genetic mutations are important risk factors for breast and ovarian cancer etiology. Women carrying one of these mutations have a high life-time risk of developing breast or ovarian cancer. The current screening strategy in Norway for women with BRCA 1/2 mutations is annual magnetic resonance imaging (MRI) and mammography from the age of 25 to 75.

The key messages in this report can be summarized as follows:

- More true positive breast cancers will be identified when MRI is used in addition to mammography (higher sensitivity), but at a cost of more false positives (lower specificity)
- We were not able to detect a decrease in breast cancer mortality when annual MRI was added to an annual mammography-screening program. The certainty of the evidence was considered very low, due to imprecision and very wide confidence interval.
- Annual savings would be approximately 6.2 million NOK if annual MRI screening of BRCA1 and BRCA2 mutation carriers was removed from the current practice and replace with mammography alone
- Annual savings would be approximately 2.5 million NOK if annual MRI screening was only offered to for BRCA1 and BRCA2 mutation carriers between 25 to 50 years of age, followed by annual mammography alone up to the age of 70

Title:

Diagnostic accuracy, clinical effectiveness and budget impact of screening BRCA1/2 mutation carriers by MRI. A health technology assessment.

Type of publication:

Health technology assessment

Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the development of safe, effective health policies that are patient-focused and that seek to achieve the best value.

Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No recommendations

Publisher:

Norwegian Institute of Public Health

Updated:

Last search for studies:
December 2016.

Executive summary

Background

The Commission forum for the Regional Health Authorities in the National System for Managed Introduction of New Health Technologies within the Specialist Health Service, commissioned a health technology assessment (HTA) of the diagnostic accuracy, clinical effectiveness and budget impact of breast cancer screening using magnetic resonance imaging (MRI) in combination with mammography, for women with BRCA1/2 genetic mutations.

BRCA1 and BRCA2 genetic mutations are important risk factors for breast and ovarian cancer. These mutations are not very common in the general population, but women carrying one of these mutations have a high life-time risk of developing breast or ovarian cancer.

Current strategies for early detection and risk reduction of breast cancer are screening using mammography and/or magnetic resonance imaging (MRI), prophylactic mastectomy and oophorectomy. While Norwegian national clinical guidelines describe prophylactic mastectomy as the best option to reduce breast cancer risk, many women in Norway prefer to have annual breast cancer screening using both mammography and MRI. It is important to assess which preventive measure is the most effective and cost-effective. This information would help determine appropriate methods for preventing and treating breast cancer among women with high breast cancer risk, and would help these women make personal choices.

Objective

The objective of this health technology assessment is to examine the diagnostic accuracy, clinical effectiveness and budget impact of breast cancer screening using magnetic resonance imaging (MRI) in combination with mammography versus mammography alone in women with BRCA1 or BRCA2 genetic mutations.

Method

We conducted systematic literature searches for systematic reviews and for primary studies. Individual search strategies were designed for each database. Search strategies were based on

a combination of subject headings and text words for BRCA, MRI and breast cancer. Two reviewers independently screened all identified records and critically appraised the selected publications. The outcomes of interest were cancer mortality and breast cancer mortality.

Quantitative data for the included studies were combined for meta-analysis using Review Manager. We report the diagnostic accuracy and used a random effects model to estimate odds ratios or risk ratios and corresponding 95 % confidence intervals. We used the GRADE tool (Grading of Recommendations Assessment Development and Evaluations) to assess the certainty of the evidence.

Health economic evaluation

In current practice, women are screened annually using MRI in combination with mammography from 25 to 75 years old. In this HTA, we compare this practice with two alternative strategies:

1) An annual screening with mammography only from age 25 to 70

2) A combination of annual MRI and mammography from age 25 to 50, followed by annual mammography alone up to age 70.

Results

The literature search was completed in December 2016, and resulted in five included references: one systematic review and four clinical studies.

Diagnostic accuracy

The combination of MRI and mammography was associated with higher sensitivity and lower specificity than mammography only. This means that more true positives will be identified (13 and 12 more per 1000 per year for BRCA1 and BRCA2, respectively) at the cost of more false positives (140 and 118 more per 1000 per year for BRCA1 and BRCA2 carriers, respectively). The certainty of the evidence was considered high.

Clinical effectiveness

We were not able to detect a reduction in breast cancer mortality when adding MRI to an annual mammography screening program compared to only mammography (RR 0.64; 95% CI 0.16-2.54). The certainty of the evidence was considered very low, due to imprecision and very wide confidence interval. The mortality of women in the non-screening group was significantly higher than for women who attended a screening program with either mammography alone or a combination of MRI and mammography.

Economical outcomes

The current breast screening strategy for BRCA1 and BRCA2 carriers is annual MRI and mammography from the age of 25 to 75. An alternative strategy examined in this report involves annual screening with mammography as currently prescribed, but MRI only from age 25 to 50, thus saving approximately 1.4 million NOK for BRCA 1 carriers and 1.1 million NOK for BRCA2 carriers each year. A further reduction in cost will be achieved by introducing a screening program involving only annual mammography compared to the current practice resulting in 6,2 million NOK annual savings for both BRCA1 and BRCA2 mutation carriers.

Discussion

The ideal way to investigate the effect of screening interventions is prospective studies starting follow-up when women are identified as mutation carriers and to follow them until potential breast cancer development. In our evaluation, only one study fulfilled this criterion. In the other studies, women were enrolled at the time of diagnosis and were retrospectively divided in groups depending on which screening regime they had been following.

Potential risk of radiation-induced breast cancer is highly relevant when choosing a screening modality for identifying breast cancers, in particular in young women carrying a mutation. However, we have not considered this in the present report.

Conclusion

Higher sensitivity but lower specificity are obtained when MRI and mammography are used in combination compared to mammography only for detection of breast cancers in BRCA1 and BRCA2 mutation carriers. Therefore, by the combined screening, more true positives will be found, but also more false positives. Adding MRI to an annual mammography-screening program has not shown to statistically significant reduce breast cancer mortality among women with hereditary breast and ovary cancer generally, or BRCA1 and BRCA2 mutations specifically, compared to mammography screening alone. The results suggests that if MRI is removed from the current Norwegian screening strategy, the consequence would be a reduction in MRI screening-related costs. Future studies should have longer follow-up and report the association between detected breast cancer, stage distribution at diagnosis and treatment costs.

Hovedfunn (norsk)

BRCA1 og BRCA2 er genetiske mutasjoner. De er viktige risikofaktorer i bryst og eggstokkreft. Mutasjonene er sjeldne i befolkningen generelt, men kvinner som bærer en av disse mutasjonene har en høy risiko for å få bryst eller eggstokkreft. Retningslinjene i Norge for kvinner med BRCA1/2 mutasjoner er tilbud om brystkreftscreening ved årlig mammografi og magnetisk resonans imaging MRI fra 25-75 år.

De viktigste funnene fra denne rapporten, er:

- Flere reelle positive vil bli funnet, men også flere falske positive vil bli funnet, dersom MRI ble brukt i tillegg til mammagrafi-screening
- Brystkreftdødelighet reduseres ikke statistisk signifikant dersom MRI blir brukt i tillegg til mammografi-screening. På grunn av bredt konfidensintervall og generelt lave dødelighetstall, har vi lav tillit til disse resultatene.
- Vi har estimert en årlig innsparing på 6,2 millioner kroner ved å fjerne tilbudet om årlig MRI fra gjeldende retningslinjer fra kvinner med BRCA1/2 mutasjoner
- Vi har estimert en årlig innsparing på 2.5 millioner kroner ved å tilby kvinner med BRCA1/2 mutasjoner et screeningprogram med årlig mammografi og MRI fra 25--50 år, og deretter bare tilby mammografi frem til 70 år.

Tittel:
Diagnostisk nøyaktighet, klinisk effekt og budsjettkonsekvensanalyse ved MRI screening av kvinner med BRCA1/2 mutasjoner.

Publikasjonstype:

Metodevurdering

En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Minst ett av følgende tillegg er også med:
Helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

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Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriterient
- Ingen anbefalinger

Hvem står bak denne rapporten?

Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum RHF

Når ble litteratursøket utført?

Søk etter studier ble avsluttet desember 2016.

Sammendrag (norsk)

Bakgrunn

Folkehelseinstituttet fikk i oppdrag av Bestillerforum RHF i Nye metoder å utføre en fullstendig metodevurdering om klinisk effekt og budsjettkonsekvensanalyse ved bruk av både magnetisk resonans imaging (MRI) og mammografi-screening av kvinner med BRCA-mutasjoner.

BRCA1 og BRCA2 er genetiske mutasjoner. De er viktige risikofaktorer i bryst og eggstokkreftetiologi. Mutasjonene er sjeldne i befolkningen generelt, men kvinner som bærer en av disse mutasjonene har en høy risiko for å få bryst eller eggstokkreft.

Tidlig oppdagelse og risikoreduksjon vil være nyttig. To strategier som foreslås for risikoreduksjon; forbyggende fjerning av bryster og eggstokker eller screening ved hjelp av MRI og / eller mammografi. Mens forebyggende fjerning av bryster (profylaktisk mastektomi) er beskrevet i norske retningslinjer som det beste alternativet for å redusere risikoen for brystkreft, foretrekker endel norske kvinner heller en årlig brystkreftscreening ved hjelp av mammografi og MRI. For å være i stand til å forebygge eller behandle brystkreft i denne gruppen av kvinner med høy risiko for brystkreft, er det viktig å finne ut hvilket forebyggende tiltak som er mest effektivt og kostnadseffektivt. I tillegg vil det hjelpe disse kvinnene med å gjøre personlige valg. Folkehelseinstituttet er blitt bedt om å vurdere klinisk effekt og gjøre en budsjettkonsekvensanalyse av brystkreftscreening ved MR eller MR og mammografi hos kvinner med BRCA1 og BRCA-genfeil.

Problemstilling

Hensikten med denne rapporten er å undersøke diagnostisk nøyaktighet, klinisk effekt samt å utføre en budsjettkonsekvensanalyse av brystkreftscreening med årlig MRI i kombinasjon med mammografi versus bare mammografi for kvinner med BRCA1 eller BRCA2 genetiske mutasjoner.

Metode

Vi søkte etter litteratur i medisinske databaser, og to forfattere gjennomgikk alle referanser for å identifisere relevante publikasjoner i henhold til forhåndsgitte kriterier. Vi innhentet fulltekst publikasjoner av potensielt relevante referanser, og vi vurderte de 5 inkluderte referansene for risiko for skjevhet i henhold til studiedesign. Én forfatter hentet ut data som deretter

ble kontrollert av en annen.

Vi analyserte resultatene ved hjelp Review Manager. Den diagnostiske nøyaktigheten ble oppsummert og odds ratio med tilhørende 95 prosent konfidensintervall for effektestimatene ble kalkulert der det var mulig å sammenligne studier. Vi brukte GRADE (Grading of Recommendations, Assessment, Development and Evaluations) for å vurdere tiltro til den diagnostisk nøyaktigheten samlet kvalitet på dokumentasjonen for hvert utfall.

Helseøkonomisk analyse
Budsjettkonsekvensanalysen sammenligner årlig MRI og mammografi for kvinner med BRCA1/2 mutasjoner, med to alternative strategier:

1) Årlig mammografi for kvinner mellom 25 og 70
2) Årlig mammografi og MRI kvinner mellom 25 og 50 år, og deretter årlig mammografi frem til fylte 70 år.

Resultat

Vi gjennomførte litteratursøket etter studier på MRI og mammografi for kvinner med BRCA 1/2 mutasjoner som ble screenet for brystkreft til og med desember 2016. Vi identifiserte 1020 referanser. Etter å ha lest titler, sammendrag og fulltekster, inkluderte vi en systematisk oversikt og fire referanser basert på tre kliniske studier.

Diagnostisk nøyaktighet
Resultatene viste at årlig MRI og mammografi gir høyere sensitivitet, men lavere spesifisitet, sammenlignet med bare årlig mammografi for denne gruppen kvinner. Dette betyr at 13 per 1000 per år flere BRCA1 og 12 per 100 per år flere BRCA2 positive brystkrefttilfeller blir funnet, samtidig med at 140 per 1000 pr år flere BRCA1 og tilsvarende 118 flere BRCA2 falske positive brystkreft tilfeller blir funnet ved at MRI benyttes. Vi har høy tillit til disse resultatene.

Klinisk effekt
Basert på de inkluderte studiene kan vi ikke konkludere om bruk av MRI i tillegg til mammografi reduserer dødeligheten av brystkreft (RR 0.64, 95%KI 0.16-2.54). På grunn av bredt konfidensintervall og generelt lave dødelighetstall, har vi lav tillit til disse resultatene.

Helseøkonomisk budsjettkonsekvensananlyse
Ifølge budsjettkonsekvensanalysen vil en strategi som involverer både årlig MRI og mammografi for kvinner med BRCA1/2 mutasjoner mellom 25 og 50 år spare omtrent 1.4 millioner kroner årlig for BRCA1 og 1.1 millioner kroner årlig for BRCA2 sammenlignet med dagen strategi. En alternativ strategi hvor kvinner kun får årlig mammografi vil gi en innsparing på totalt 6.2 millioner kroner for både BRAC1 og BRCA2.

Diskusjon

Den ideelle måten å undersøke effekten av screeningsintervensjoner på, er prospektive studier som starter når kvinner identifiseres som mutasjonsbærere eller av sin familiehistorie. I vår evaluering oppfyller bare en studie disse kriteriene. I de andre studiene ble kvinner innlemmet i studiene på diagnosetidspunktet og delt i grupper avhengig av hvilket screeningsregime de

hadde fått. I denne rapporten har vi ikke diskutert risikoen for strålingsindusert brystkreft hos unge mutasjonsbærere.

Konklusjon

For kvinner med BRCA1/2 mutasjoner vil en kombinasjon av både MRI og mammografi i et brystkreftscreeningprogram gir høyere sensitivitet, men lavere spesifisitet, enn kun mammografi. Det betyr at flere reelle positive brystkrefttilfeller vil bli funnet, men også flere falske positive. Forskning gjort på sammenligning av dødelighet mellom disse to screeningprogrammene, viser derimot ingen sikker assosiasjon mellom screeningmodalitet og dødelighet. Det vil si at konsekvensene ved å fjerne MRI fra det norske screeningprogrammet vil gi besparelser tilsvarende MRI-kostnadene, uten at brystkreftdødeligheten går opp. Det vi ikke har funnet resultat på og hvor det trenges flere studier, er sammenhengen mellom oppdaget brystkreft, fordeling av brystkreftstadium ved diagnose, og behandlingskostnader.

Glossary and abbreviations	
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
HBOC	**Hereditary breast–ovarian cancer**
HTA	**Health Technology Assessment**
MRI	**Magnetic resonance imaging**
Odds	The odds of an event happening is defined as the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.
OR	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
RCT	**Randomized controlled trial.** An experiment in which investigators use randomization to allocate participants into the groups that are being compared. Allocation is usually made at the level of individual, but sometimes is done at the group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.
SR	**Systematic review.** A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.
Statistically significant	**Statistically significant** means that the findings of a study are unlikely to have arisen due to chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.

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Preface

The Commission forum for Regional Health Authorities (RHA) in the National System for Managed Introduction of New Health Technologies within the Specialist Health Service (Bestillerforum), commissioned a health technology assessment (HTA) for the clinical effectiveness and the budget impact of breast cancer screening using magnetic resonance imaging (MRI) alone or in combination with mammography in women with BRCA1/2 genetic mutations. The results will be used as scientific documentation in preparation for updating the Norwegian national guidelines.

Elisabeth Couto later replaced by Lene Juvet, was lead reviewer for the clinical evaluation and Einar Torkilseng, followed by Espen Movik, led the health economic evaluation. A delay in preparing the report was due to the fact that employees have terminated their employment relationship with FHI.

Following external experts were consulted throughout the process (listed alphabetically):

- Jack G Andersen, Spes. konsulent økonomi, Klinikk for radiologi og nukleærmedisin, Oslo universitetssykehus
- Hildegunn Høberg-Vetti, Overlege, Regionalt kompetansesenter for arvelig kreft, Haukeland universitetssykehus
- Trond Ludvigsen, Genetisk veileder, Medisinsk genetisk poliklinikk, St Olavs Hospital
- Lovise Olaug Mæhle, Overlege , Seksjon for arvelig kreft, Oslo universitetssykehus

Ellen Schlichting, Seksjonsleder Seksjon for bryst- og endokrinkirurgi Avdeling, for kreftbehandling, Oslo universitetssykehus and Turid Aas, MD, Department of Breast and Endocrine Surgery, Haukeland University Hospital performed peer review of the report.

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues such as clinical experience and patient preference.

Kjetil Brurberg	Lene K. Juvet	Torunn E. Tjelle	Einar Torkilseng
Scientific director	*Department director*	*Lead reviewer, Clinical evaluation*	*Lead health economist*

Objective

The objective of this health technology assessment is to examine the diagnostic accuracy, clinical effectiveness and budget impact of breast cancer screening using magnetic resonance imaging (MRI) in combination with mammography versus mammography alone in women with known BRCA1 or BRCA2 genetic mutations.

The current screening strategy in Norway for women with BRCA 1/2 mutations is annual MRI and mammography from the age of 25 to 75. In this report, we compare this practice with two alternative breast cancer screening strategies:

- Annual screening with mammography only from age 25 to 70
- Annual screening by MRI and mammography from age 25 to 50, followed by annual mammography alone up to the age of 70

Background

Screening for breast cancer

Guidelines for breast cancer screening in average-risk women in many western countries, included Norway, recommend bi-annual mammography for women above a certain age (varying from 40-55 years). A recent report from the U.S. Preventive Services Task Force concludes that breast cancer mortality is reduced with mammography screening, although estimates are of borderline statistical significance and the magnitudes of effect are small for younger ages (1).

BRCA1 and BRCA2 mutations in breast cancer etiology

Up to 10% of breast cancers are thought to result from a genetic predisposition to the disease (2;3). BRCA1 and BRCA2 genetic mutations are important risk factors for breast cancer etiology. A mutation in these tumor suppressor genes disposes a patient to an earlier appearance of breast cancer and/or ovarian cancer and an increased lifetime prevalence of developing those and other associated cancer entities. These "breast cancer genes" were identified in 1994 (4) and in 1995 (5), respectively. BRCA1 and BRCA2 genes are tumor suppressor genes (6-9).

These mutations are not very common in the general population, with an overall prevalence of *BRCA1/2* mutations reported to be from 1/400 to 1/800 (10-12). A systematic review of international studies reported prevalence rates for BRCA1 and BRCA2 mutations in breast cancer and ovarian cancers (13). In breast cancer cases unselected for age at diagnosis, prevalence rates ranged from 1.1% to 2.6% for BRCA1 mutations and were reported to be 1.1% for BRCA2 mutations. Among ovarian cancers, unselected for age at diagnosis and family history, prevalence rates ranged from 1.9 to 9.6% for BRCA1 mutations, and from 1.3% to 3.9% for BRCA2 mutations (13). In Norway, estimates indicate that 2% of breast cancer cases carry a BRCA1 or BRCA2 mutation, and that 23% of ovarian cancers have a BRCA1 or BRCA2 mutation (14).

Women carrying a BRCA1 or BRCA2 genetic mutation have a high lifetime risk of developing breast or ovarian cancers. A published combined analysis of 22 studies reported cumulative breast cancer risks by age 70 of 65% (95% CI: 51-75%), and 45% (95% CI: 33-54) for BRCA1 and BRCA2 mutations carriers, respectively (15). For ovarian cancer, the cumulative risk by age 70 was 39% (95% CI:22-51%) for BRCA1 mutation carriers, and 11% (95% CI: 4.1-18) for BRCA2 mutation carriers (15). ***Table 1*** summarizes the likelihood of detecting BRCA1 or BRCA2 mutations in individuals unselected for family history (16).

Table 1. *Frequency of BRCA mutation in breast cancers*

Individuals	Frequency of a BRCA mutation
If a woman is diagnosed with breast cancer	
<30-40 years old	~6-18%
<45-50 years old	~6%
Any age	~2%
And with triple-negative histology	~9-28%
If a man is diagnosed with breast cancer	
Any age	~4-14%

In Norway, 3 439 cases of breast cancers and 669 breast cancer deaths were reported in 2015 (17). For ovarian cancer, corresponding numbers were 504 and 297. In 2015, 16 109 individuals were living with diagnosed breast cancer, and corresponding numbers for ovarian cancer were 2 398 (17). Many survive breast cancer and in 2015, the number of living person who had previously had breast cancer were 44 182. For ovarian cancer, the number was 4 575 (17).

Breast cancer tends to develop at a younger age in BRCA carriers than the general population (18). BRCA1-related breast cancers are often more aggressive and have a worse outcome than non-hereditary tumors (i.e. tumors not known to be related to a genetic mutation) (19). For BRCA2-related breast cancers, the evidence is less conclusive (19).

Women with a familial risk of breast cancer can be tested for BRCA1 and BRCA2 mutations. In Norway, the following criteria are used for testing these mutations (20):

- to be younger than 50 at breast cancer diagnosis
- to have two close relatives diagnosed with breast cancer at an average diagnosis age below 55
- to have three close relatives diagnosed with breast cancer (independent of age at diagnosis)
- to be a man diagnosed with breast cancer
- to have bilateral breast cancer below 60 years old
- to have had breast cancer and a close relative with ovarian cancer
- to have had breast cancer and a close relative with prostate cancer diagnosed below 55 years old
- to have a diagnosis of ovarian cancer

Most of these criteria are based on familial breast or ovarian cancer background. There are several scores that can help identify women with high risk of breast cancer (21-23). These are most commonly based on women's genetic background (e.g. family structure, relative's age at diagnosis).

Strategies offered to women carrying a BRCA1 or BRCA2 mutation

Norwegian guidelines propose two strategies for women with known BRCA1 or BRCA2 mutations: risk reducing interventions (e.g. prophylactic surgeries) or extensive surveillance (20).

Prophylactic surgeries

In Norway, women with BRCA1 or BRCA2 mutations should be informed that prophylactic mastectomy is the most efficient strategy, with a reduction in breast cancer risk of 90 to 98% (20). Clinicians should also inform women carrying these mutations about the benefits of prophylactic bilateral salphingo-oophorectomy (20).

Extensive surveillance

In Norway, like in several other countries, women with a high risk of breast cancer who do not wish to opt for prophylactic mastectomy are offered annual breast cancer screening by MRI and a limited version of mammography imaging (mediolateral oblique view (MLO) (20). As mentioned above, women with BRCA1 or BRCA2 mutations tend to develop breast cancer at earlier ages. Younger women have denser breast tissue making the detection of breast cancers more difficult.

To date, it is not clear which strategy is most efficient in reducing mortality: MRI alone or in combination with mammography, or mammography alone. To be able to adequately prevent or treat breast cancer in this group of women with high breast cancer risk, it is important to ascertain which preventive measure is most efficacious.

Screening procedures in high-risk women is not as clear. In the UK, women with medium and high risk are offered annual mammography from the age of 40 and annual MRI from the age of 30 until 49 years. After 50, these women are recommended to enter the general breast cancer screening program (bi-annual mammography) (24). American Cancer Society screening recommendations for women at higher than average risk of breast cancer involve MRI and a mammogram every year after age 30 (25). According to the Norwegian guidelines, women with detected mutations for penetrant cancers are offered annual MRI from 25 years (20). MRI controls should be offered routinely up to the age of 75, if no risk-reducing mastectomy is performed, then a radiological assessment is made of which controls should be offered further up to the age of 80.

Priority setting criteria

According to Norwegian policy documents (26), a treatment should be prioritized if the following criteria are met:

1. *The disease is severe;* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual

in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective;* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective;* the added costs of the treatment should be reasonable compared to the added benefits.

The policy documents mentioned above provide no guidance as to what constitutes a reasonable relationship between cost and effectiveness.

Aim of this health technology assessment

The objective of this health technology assessment is to examine the clinical effectiveness and budget impact of breast cancer screening using magnetic resonance imaging (MRI) in combination with mammography versus mammography alone in women with known BRCA1 or BRCA2 genetic mutations. The recommendation of the National Institute for Health and Care Excellence (NICE) (24) is to offer annual MRI surveillance to women aged 30–49 years with a known BRCA1 or BRCA2 mutation, and is the basis of the two comparators in budget impact model .

Currently, BRCA1 and BRCA2 mutation carriers are screened annually with MRI in combination with mammography from the age of 25 until they are 70 years old. In this report, we compare this practice with two alternative breast cancer screening strategies:

- Annual screening with mammography only from age 25 to 70
- Annual screening by MRI and mammography from age 25 to 50, followed by annual mammography alone up to the age of 70

Methods

Inclusion and exclusion criteria for literature search

Studies of diagnostic accuracy for mammography and MRI and clinical effectiveness were included:

Population

Women aged 18 and above who have a high risk of breast cancer called hereditary breast and ovary cancer (HBOC), (studies that included women who have or possibly have a BRCA1 or BRCA2 genetic mutation were eligible).

Interventions

The intervention of interest was screening for breast cancer using MRI in combination with mammography.

Comparison

We assessed studies examining this intervention in comparison with no intervention or mammography alone.

Outcome

Our main aim was to include studies examining the following outcomes:

- Overall mortality
- Overall cancer mortality
- Breast cancer mortality
- Sensitivity, specificity, true positive, false positive

Study design

Eligible study designs were health technology assessments (HTA), systematic reviews (SR), randomized controlled trials (RCT), and prospective cohort studies with a control group. We searched for HTA reports and systematic reviews (SR) that addressed our objectives. If our specified outcomes were not available in the identified HTA reports or SRs, we used primary studies to cover those endpoints. Studies were considered prospective if data on intervention (or exposure) were collected or measured prior to outcome data ascertainment.

Literature search

We searched systematically for literature in the following databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- Embase 1980 to present
- Cochrane Library; Cochrane Database of Systematic Reviews, Other Reviews, Technology Assessments, Cochrane Central Register of Controlled Trials (Central)
- Centre for Reviews and Dissemination: Database of Abstracts of Reviews of Effects , Health Technology Assessment Database, NHS Economic Evaluation Database
- Web of Science
- PubMed (epub ahead of print)

The search strategy was designed, peer reviewed and executed by two experienced information specialists in collaboration with the research team (see Appendix 1). The search included used index terms and free text terms describing the population and intervention of interest (e.g. Breast cancer, BRCA1, BRCA2, Magnetic Resonance Imaging and Mammography). The search was adapted to each database and had no language restrictions. We primarily searched for systematic reviews and subsequently for primary studies for additional studies of newer date.

Two authors independently screened the title and abstract of the retrieved records for inclusion based on the eligibility criteria. A third author resolved differences in the two authors' selection of included records. We screened relevant papers found in reference lists of selected articles and searched Clinical Trials.gov to identify relevant ongoing trials.

Data collection and analysis

Selection of studies

Articles were selected following a two-step strategy:

1) Two review authors conducted a preliminary screening by independently assessing titles and abstracts of retrieved articles to identify relevant full-length articles for further examination.
2) Full-length articles were then read independently by two persons to decide which articles to include in the systematic review. Both steps were carried out considering the inclusion criteria. Disagreement at either stage was settled by discussion or consultation with a third person. If needed, publication authors were contacted to obtain further information.

Data extraction and management

One review author extracted the data from individual studies. Another verified the data. When relevant and possible, we extracted the following information: publication citation; clinical trial information; information on methods (i.e., study design, sequence generation, allocation, blinding); participants (i.e., numbers, setting, age, sex, country); and description of intervention/exposure, and comparison groups (i.e., numbers, definition, methods used to ascertain exposure

and control, frequency of intervention/exposure and comparison). We also collected data on outcomes (i.e., ascertainment methods, numbers, follow-up time), and results (i.e., estimate of effect, statistical methods used, confounding factors considered).

Assessment of risk of bias in included studies

We assessed risk of bias of prospective cohort studies using the Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) (27). The tool identifies bias associated with the following domains: confounding, selection of participants into the study, measurement of interventions, departures from intended interventions, missing data, measurement of outcomes and selection of the reported results. Risk of bias could be classified as low, moderate, serious, critical, or under the category "not enough information". When using this tool, one should define *apriori* the critically important confounding factors that prospective cohort studies should have taken into account. Prior to assessing risk of bias in any of the included studies, we defined age, socioeconomic factors, frequency of screening, and treatment received as critically important confounding factors. For systematic reviews, the Critical Appraisal Skills Program (CASP) Systematic Review Checklist 13.03.17, was used (http://www.casp-uk.net/casp-tools-checklists).

Two review authors carried out risk of bias assessment independently and then jointly. We resolved any assessment discrepancies through discussion and by consulting the study's publication authors.

Statistical analysis and presentation of results

Effect measurement and data synthesis

Quantitative data for the included cohort studies were combined for meta-analysis using Review Manager (RevMan version 5.3). We calculated odds ratios for our primary outcomes (overall mortality, cancer mortality and breast cancer mortality) in the intervention group compared to the control group. We did not analyze the results on diagnostic accuracy, but rather used them as they were presented in the systematic review.

Assessment of heterogeneity

We assessed heterogeneity among included studies by calculating the I^2 statistic (28) with RevMan. I^2 statistics and corresponding p-values are presented. We adopted the levels of I^2 suggested by the Cochrane Handbook for Systematic Reviews of Interventions (I^2 values of 0%, 25%, 50% and 75% represented no, low, moderate and high heterogeneity, respectively). The threshold for interpreting the I^2 value can be misleading; therefore, we determined the importance of the observed I^2 value by looking at the magnitude and direction of the effect as well as at the strength of evidence for clinical heterogeneity.

Grading the quality of evidence

Two review authors independently assessed the quality of the evidence for each outcome. The certainty of the evidence was evaluated using GRADE (Grading of Recommendations, Assessment, Development, and Evaluations). GRADE specifies the following criteria when rating the quality of evidence: study design (risk of bias criteria), inconsistency of the results (heterogeneity), indirectness (applicability), imprecision of estimates, and publication bias. The overall quality of the evidence was classified into four possible categories described in *Table 2*.

Table 2. *Definition of each assessment category in GRADE (GRADE Working Group grades of evidence)*

Grade	Definition
High certainty	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different
Low certainty	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Changes from the study protocol

There have been minor changes from the study protocol, listed below:

- We included diagnostic accuracy as an outcome. This was important for the budget impact analyses as none of the breast cancer mortality numbers could be used.
- Results based on MRI alone were not included because the standard screening I Norway includes mammography.
- Overall mortality was not mention in the outcomes due to this number would be the same as cancer mortality in our included studies.

Clinical evaluation – Results

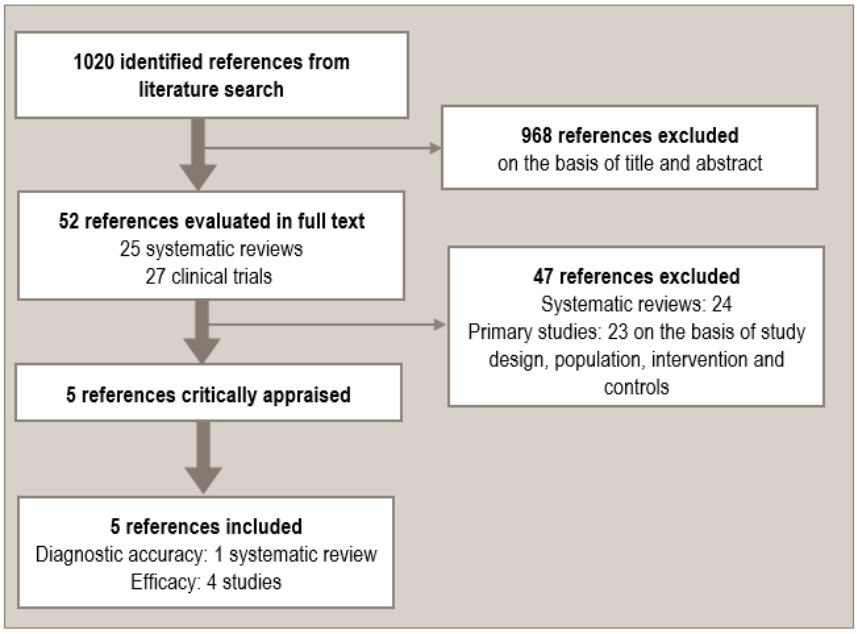
Result of literature search

The literature search for studies on breast cancer screening using MRI in addition to mammography for BRCA positive women was performed in three steps:

First, we searched for systematic reviews without limiting the search to year of publication (2015.04.16). We identified 25 relevant references for full text reading. Only one of the references had a relevant systematic search. It was a health technology assessment (HTA) from Canada published in 2010 (29). This HTA completed a search for primary studies about breast cancer mortality in women undergoing different screening programs in March 2010. Their search identified no relevant studies and thus the HTA was not included in this report. Secondly, we searched for controlled trials (2016.01.25) and limited the search to year of publication from 2010 and onward, based on the empty search results in the Canadian HTA. Finally, we updated our literature search for systematic reviews because of delay in the project progress. The final search was completed in December 2016 (see Appendix 1 for search strategy).

In total, we identified 1020 references all together in the three searches. We excluded 968 references based on the titles and abstracts. A total of 52 references were considered eligible and read in full text. We excluded 47 references of which 24 were systematic reviews and 23 primary studies (Appendix 2). We examined five references for the present report: one systematic review (30) and four clinical trials (31-34). A flow diagram of the selection process is shown in *Figure 1*.

Figure 1. *Flowchart of identification of documentation*



Included systematic review about diagnostic accuracy

We identified one systematic review on diagnostic accuracy (specificity and sensitivity of screening modalities). The systematic review was a meta-analysis of individual patient data from six high-breast-cancer-risk screening trials in which MRI's additional contribution to mammography was investigated (30). The systematic review was of high quality and published in 2016 (Appendix 3).

Included studies about clinical effectiveness

Study characteristics

The four included observational studies (31-34) are described in detail in *Table 3* and Appendix 3. Data from one cohort was presented in two different papers (32;33), hence, we only included the additional cohort (the Oslo population) in the newest reference (32) to avoid using the same population twice.

Location: The studies were conducted in France (31), Netherlands (34), United Kingdom (33) and Norway (32).

Mutations: Study participants were women with known BRCA 1 and 2 mutation or other familial risks such as hereditary breast and ovary cancer (HBOC). The grouping of mutations was not completely overlapping between the studies. The mutation status/other familial risks were determined either at the time of entering the screening or at the time of diagnosis.

Age: Women included in the studies were between 20 and 70 years old.

Timing of enrollment in study: One study enrolled the subjects at the initiation of the screening programs (33). Three studies selected women at the time of breast cancer diagnosis and

grouped them according to which surveillance they had undergone previously (31;32;34). The follow-up time was 3 to 11 years from breast cancer diagnosis. The authors define these studies as prospective studies although the screening program had started before the study initiated. However, the follow up from breast cancer diagnosis to the time of death was prospective.

Table 3. *Included studies in this report*

Study name		MARIBS	MRISC
	Chereau 2010 (31)	Evans 2014 and 2016 (32;33)	Saadatmand 2015 (34)
Study design	Prospective study (follow up survival after diagnosis)	Prospective cohort (follow up survival after initiation of screening program)	Prospective cohort with matched controls (follow up survival after diagnosis)
Enrollment in MRI screening program	2001-2007 France	1997-2004 (MARIBS) UK 2006-2013 (NICE) UK 1990-2014 (Oslo) Norway	1999-2007 Netherlands
Enrollment in the study	Breast cancer patients carrying BRCA1/2 Diagnosed with cancer 2001-2007	When enrolled in the screening program. Subsequently, breast cancer patients with predisposition were recorded. Intervention group: 1997-2004 Control group: Not mentioned Diagnosed with cancer: Intervention group: not mentioned Control group: 1990-2013	Breast cancer patients with predisposition Diagnosed with cancer 1999-2009
Age	20-70 years	35-55 years	26-68 years
Follow up time from diagnosis of cancer	2.7 years in intensive screening program vs 4.2 years outside these screening programs	11.75 MRI vs 6.6 years 11.75 median follow up time in the MRI group vs 6.6 years follow up in the mammography group from the time of diagnosis	Median follow up of 9 years

The studies were assessed to have high risk of bias, mainly due to unclear allocation concealment and unclear blinding. The risk of bias assessments for the included references are shown in Appendix 3.

Description of available comparisons

In the following, intervention groups are labelled "*MRI+*" and refer to MRI and mammography screening annually to women with high risk of breast cancer.

In our analyses, we defined the control group in Saadatmand 2015 (34) as a "no screening" group although women from 50 years and above were offered mammography following national guidelines. We assume that most of the women in this group had not undergone biannual screening as Saadatmand 2015 (34) reported a median age for women at breast cancer diagnosis to be 44 years.

In addition, we differentiated the analysis according to whether the women were aware of their mutation status (BRCA1/2) or if they were in a familial risk group (HBOC).

The included studies have different follow-up times after breast cancer diagnosis (3-11 years), but we analyzed them together because of the low number of available studies. Two studies reported breast cancer mortality (or cancer mortality) after the women entered a screening program (32;33) and two studies initiated the follow-up period after the women were diagnosed with breast cancer (31;34). Two of the studies had biannual ultrasound or clinical breast examination in addition to MRI and mammography (31;34).

In this report, we have compared the following groups (see detailed description in *Table 4*):

1. MRI+ *versus* mammography (results from 2 papers (31-33))
2. MRI+ *versus* no screening (results from 2 papers (32-34))

Table 4. *Definition of groups in the different studies including study subjects*

	MRI+	Mammography	No screening*
Chereau 2010 (31)	BRCA1/2 carriers aware of their mutation status under screening program including annual digital mammography, biannual ultrasound and physical examination, or annual MRI	Hereditary breast cancer not aware of BRCA1/2 carriers not aware of their mutation status outside intensive screening program, but annual mammography, biannual ultrasound and physical examination	
Evans 2014 and 2016 (32;33)	Proven or likely proven mutant carriers (BRCA1/2 or other mutants) under either of the screening programs: Subset 1: annual MRI (MARIBES) Subset 2: annual MRI and mammography (6 months apart) (NICE) Subset 3: annual MRI and mammography (Oslo)	Hereditary breast cancer Mutation carriers not aware of their mutation status but at risk, under yearly mammography screening program.	BRCA1/2 carriers not aware of their mutation status, a subset aged 50-55 years had 3 yearly mammograms.
Saadatmand 2015 (34)	Subjects aware of their mutation status (BRCA1/2) or other with familial risks under screening program including clinical breast examination 6-month, annual mammography and annual MRI		Matched controls not aware of their mutation status, with biannual mammography if 50 years or older

** Note that we use the expression "no screening" although this group had a limited screening after reaching 50 years*

Diagnostic accuracy of MRI and mammography screening for breast cancer

According to the included systematic review on diagnostic accuracy, in BRCA1 mutation carriers of all ages (n=1219), adding MRI to mammography significantly increased screening sensitivity, but specificity was reduced (30). The annual incidence of breast cancer in a Norwegian BRCA 1 population has been estimated by Møller et al. (39). *Table 17* presents all these estimates and shows that the incidence increases with age and peaks at around age 40 to 49 when it reaches 2,2%. We are not aware of any similar estimates for the BRCA 2 population in Norway, and therefore applied the BRCA 1 rates to both BRCA populations. Thus, the present screening program with MRI and mammography in a Norwegian setting, detects 12 per 1000 more true positives and 118 per 1000 more false positives per year in the age group 40-49 years, compared to a screening program with mammography only (*Table 5*). The certainty of evidence was considered as high.

Table 5.*Certainty of evidence: Should MRI and mammography vs. mammography be used to diagnose breast cancer in BRCA1 mutation carriers?*

Patient or population : BRCA 1 age group 41-50 years
Pooled sensitivity MRI + mammography: 0.94 (95% CI: 0.75 to 0.99)
Pooled specificity MRI + mammography: 0.77 (95% CI: 0.71 to 0.83)
Pooled sensitivity mammography: 0.34 (95% CI: 0.21 to 0.51)
Pooled specificity mammography: 0.92 (95% CI: 0.87 to 0.95)

Test result	Number of results per 1 000 patients tested (95% CI)		Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 2,2% Typically seen in BRCA1			
	MRI + mammography	mammography		
True positives	**21** (16 to 22)	**8** (5 to 11)	1219 (6)	⊕⊕⊕⊕ **HIGH**
	13 more TP in MRI + mammography			
False negatives	**1** (0 to 6)	**14** (11 to 17)		
	13 fewer FN in MRI + mammography			
True negatives	**755** (689 to 810)	**895** (848 to 925)	1219 (6)	⊕⊕⊕⊕ **HIGH**
	140 fewer TN in MRI + mammography			
False positives	**223** (168 to 289)	**83** (53 to 130)		
	140 more FP in MRI + mammography			

CI: Confidence interval, FN: false negative; FP: false positive

In BRCA2 mutation carriers of all ages (n=732), adding MRI to mammography significantly increased screening sensitivity, but specificity was reduced. Thus, the present screening program with MRI and mammography in a Norwegian setting, detects 13 per 1000 more true positives and 140 per 1000 more false positive per year in the age group 40-49 years, compared to a screening program with mammography only (*Table 6*). The certainty of evidence was considered as high.

Table 6. *Certainty of evidence: Should MRI and mammography vs. mammography be used to diagnose breast cancer in BRCA2 mutation carriers?*

Patient or population : BRCA2 age group 41-50 years
Pooled sensitivity MRI + mammography : 0.91 (95% CI: 0.70 to 0.98)
Pooled specificity MRI + mammography : 0.80 (95% CI: 0.73 to 0.85)
Pooled sensitivity mammography : 0.38 (95% CI: 0.22 to 0.56)
Pooled specificity mammography : 0.92 (95% CI: 0.87 to 0.95)

Test result	Number of results per 1 000 patients tested (95% CI)		Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 2.2% Typically seen in BRCA 1*			
	MRI + mammography	mammography		
True positives	20 (15 to 22)	8 (5 to 12)	732 (6)	⊕⊕⊕⊕ HIGH
	12 more TP in MRI + mammography			
False negatives	2 (0 to 7)	14 (10 to 17)		
	12 fewer FN in MRI + mammography			
True negatives	782 (717 to 834)	900 (851 to 931)	732 (6)	⊕⊕⊕⊕ HIGH
	118 fewer TN in MRI + mammography			
False positives	196 (144 to 261)	78 (47 to 127)		
	118 more FP in MRI + mammography			

* As no prevalence data was found for BRCA 2,we used the same prevalence as for BRCA1

CI: Confidence interval, FN: false negative; FP: false positive

Effectiveness of MRI+ in asymptomatic women with HBOC

To understand the impact of using MRI+ to decrease cancer mortality in women with HBOC we analyzed available data where this group of women were enrolled in different screening programs. Only one true prospective study for this outcome was available (33).

MRI+ *versus* no screening program for asymptomatic women with HBOC

None of the included studies reported data on MRI+ *versus* no screening in comparable groups.

MRI+ *versus* mammography screening program for asymptomatic women with HBOC

The only study available was not able to detect a difference in overall cancer mortality between asymptomatic women with HBOC who were enrolled in the MRI+ group and those who only received mammography (RR=0.71; 95%CI=0.24, 2.11; P=0.54) (*Figure 2*). Similar results were seen for breast cancer mortality (RR=0.64; 95%CI=0.16, 2.54; P=0.52) (*Figure 2*). The certainty of evidence was considered very low as the data were based on a single observational study and further downgraded due to the wide confidence interval (*Table 7*).

This study also included data on breast cancer incidences in the screened population. The results show no difference in the detection of breast cancers through the different screening programs (MRI+ versus mammography) (RR=1.06; 95%CI=0.77, 1.46; P=0.74) (*Figure 2*).

Figure 2. *Cancer incidences and mortality among asymptomatic women with HBOC: MRI+ versus mammography*

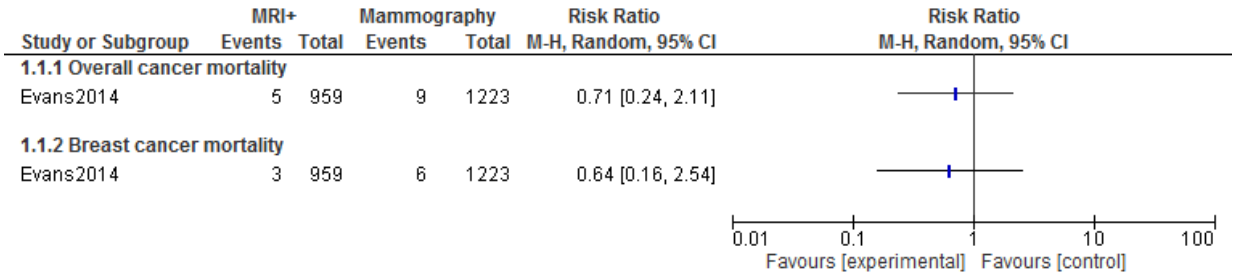


Table 7. *Certainty of evidence for MRI+ compared to mammography for screening of asymptomatic women with HBOC*

Patient or population: Asymptomatic women with HBOC
Intervention: MRI and mammography
Comparison: Mammography

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with mammography	Risk with MRI + mammography			
Overall cancer mortality	7 per 1 000	5 per 1 000 (2 to 16)	RR 0.71 (0.24 to 2.11)	2182 (1 observational study)	⨁◯◯◯ VERY LOW [a]
Breast cancer mortality	5 per 1 000	3 per 1 000 (1 to 12)	RR 0.64 (0.16 to 2.54)	2182 (1 observational study)	⨁◯◯◯ VERY LOW [a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio
a. Wide confidence interval

Effectiveness of MRI+ in women with HBOC

An alternative approach to study the impact of using MRI+ to prevent cancer mortality in women with HBOC, is to group breast cancer diagnosed women according to their screening history, and then follow up for cancer mortality prospectively. Typically, subjects in the MRI+ group were predisposed to breast cancer due to either known BRCA1/2 mutations or other familial risk factors and therefore enrolled in such a screening program. Women in the mammography and no screening (see definition in *Table 4*) groups had their mutation status revealed after their breast cancer diagnosis.

Evans et al (35) and Saadatmand et al (34) presented this kind of partly prospective studies and followed the study subjects for 2.7 years and 9 years after breast cancer diagnosis, respectively.

We analyzed the two comparisons available: MRI+ screening program *versus* breast cancer patients under no screening programs, and *versus* mammography only.

MRI+ *versus* no screening program

Only one study reported causes other than breast cancer deaths among women with HBOC diagnosed with breast cancer during a screening program (33). Cancer mortality was significantly lower in the MRI+ group when compared with the no screening group (RR=0.37; 95%CI=0.16, 0.86; P=0.02) (*Figure 3*). Similar results were found when analyzing data on breast cancer mortality based on two studies (33;34) (RR=0.41; 95%CI=0.18 0.92; P=0.03) (*Figure 3*). The certainty of the evidence was considered low as the data were derived from cohort studies (*Table 8*).

Figure 3. *Cancer mortality among women with HBOC: MRI+ versus no screening groups*

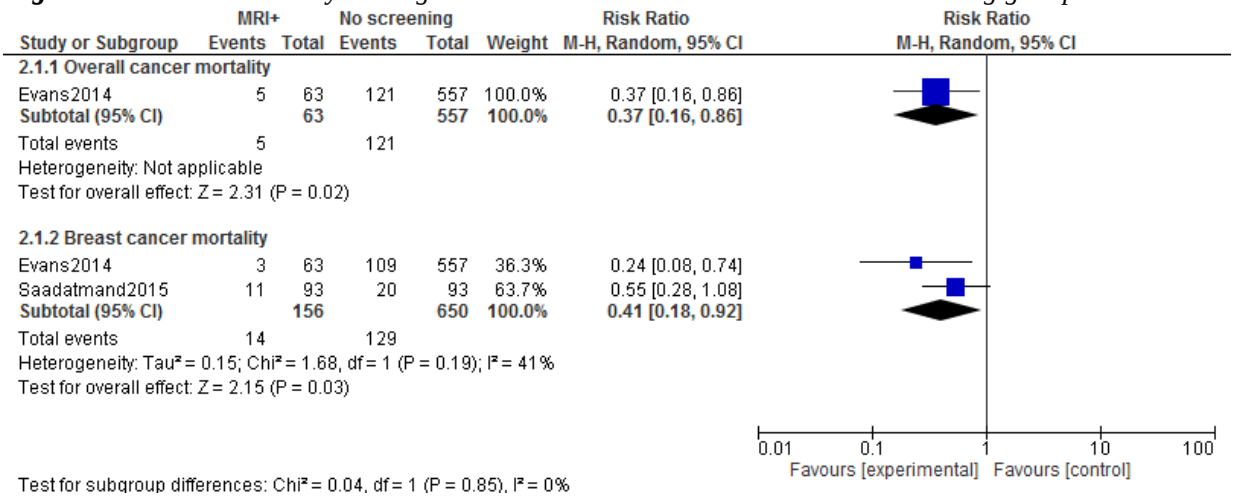


Table 8. *Certainty of evidence of mortality among women with HBOC: MRI+ compared to no screening*

Patient or population: Women with HBOC
Intervention: MRI and mammography
Comparison: No screening

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no screening	Risk with MRI + mammography			
Overall cancer mortality	217 per 1 000	80 per 1 000 (35 to 187)	RR 0.37 (0.16 to 0.86)	620 (1 observational study)	⨁⨁◯◯ LOW
Breast cancer mortality	198 per 1 000	81 per 1 000 (36 to 183)	RR 0.41 (0.18 to 0.92)	806 (2 observational studies)	⨁⨁◯◯ LOW

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio

MRI+ *versus* mammography screening program

Evans et al (33) compared breast cancer mortality among women with HBOC diagnosed with breast cancer during a MRI+ screening program with a mammography screening program. The addition of MRI to mammography in a yearly screening program did not have any significant impact neither on overall cancer mortality (RR=0.67; 0.24, 1.90; P=0.45) or breast cancer mortality (RR=0.60; 95%CI= 0.16, 2.32; P=0.46) (*Figure 4*). The certainty of the evidence was considered very low as the data were generated through cohort studies, and was further downgraded as the results had wide confidence intervals (*Table 9)*.

Figure 4. *Cancer mortality among women with HBOC: MRI+ versus mammography groups*

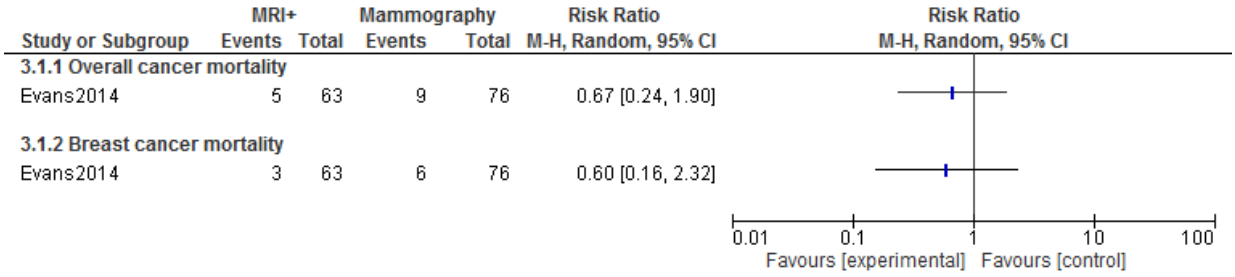


Table 9. *Certainty of evidence of mortality among women with HBOC: MRI+ compared to mammography for screening*

Patient or population: Women with HBOC
Intervention: MRI and mammography
Comparison: Mammography

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with mammography	Risk with MRI + mammography			
Overall cancer mortality	118 per 1 000	79 per 1 000 (28 to 225)	RR 0.67 (0.24 to 1.90)	139 (1 observational study)	⊕◯◯◯ VERY LOW [a]
Breast cancer mortality	79 per 1 000	47 per 1 000 (13 to 183)	RR 0.58 (0.14 to 2.32)	139 (1 observational study)	⊕◯◯◯ VERY LOW [a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio
a. Wide confidence interval

Effectiveness of MRI+ in women with BRCA1/2 mutations

The three included cohorts studying the impact of using MRI+ to prevent cancer mortality in women with BRCA1/2 mutations, grouped breast cancer diagnosed women according to their screening history, and then followed them prospectively and recorded cancer mortality.

MRI+ *versus* no screening program

Comparing breast cancer mortality among BRCA1/2 mutation carriers undergoing an MRI+ screening program with no screening program showed significant favorable results for women

in the MRI+ group (RR=0.34; 95%CI=0.15, 0.75; P=0.007) (*Figure 5*). The certainty of the evidence was considered low as data sets were generated through cohort studies (*Table 10*).

Figure 5. *Breast cancer mortality among women with BRCA1/2 mutations: MRI+ versus no screening groups*

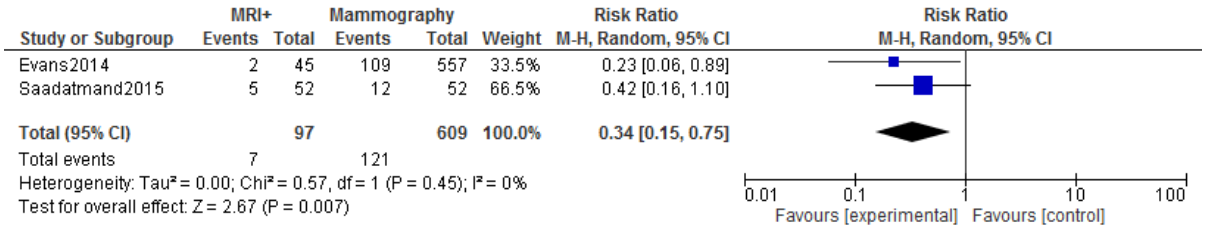


Table 10. *Certainty of evidence of mortality among women with BRCA1/2 mutations: MRI+ compared to no screening*

Patient or population: Women with BRCA1/2 mutation
Intervention: MRI and mammography
Comparison: No screening

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no screening	Risk with MRI + mammography			
Breast cancer mortality	199 per 1 000	68 per 1 000 (30 to 149)	RR 0.28 (0.15 to 0.75)	706 (2 observational studies)	⨁⨁◯◯ LOW

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio

MRI+ *versus* mammography screening program

The same benefit of reduced risk of breast cancer mortality was not seen when comparing the MRI+ group with the mammography screening group (RR=0.43; 95%CI=0.10, 1.77; P=0.24) (*Figure 6*). The certainty of the evidence was considered very low as the data sets were generated through cohort studies and further downgraded to very low due to the high confidence interval (Table 11).

Three studies reported on BRCA2 mutants separately allowing us to compare MRI+ vs mammography comparison only in BRCA2 mutation carriers. The results showed no significant difference in mortality between the screening groups (RR=0.46; 95%CI=0.12, 1.67; P=0.24) (*Figure 6*). The certainty of evidence was considered very low as the data were generated through cohort studies and the results had wide confidence intervals (*Table 11*).

Figure 6. *Breast cancer mortality among women with BRCA1/2 mutation: MRI+ versus mammography*

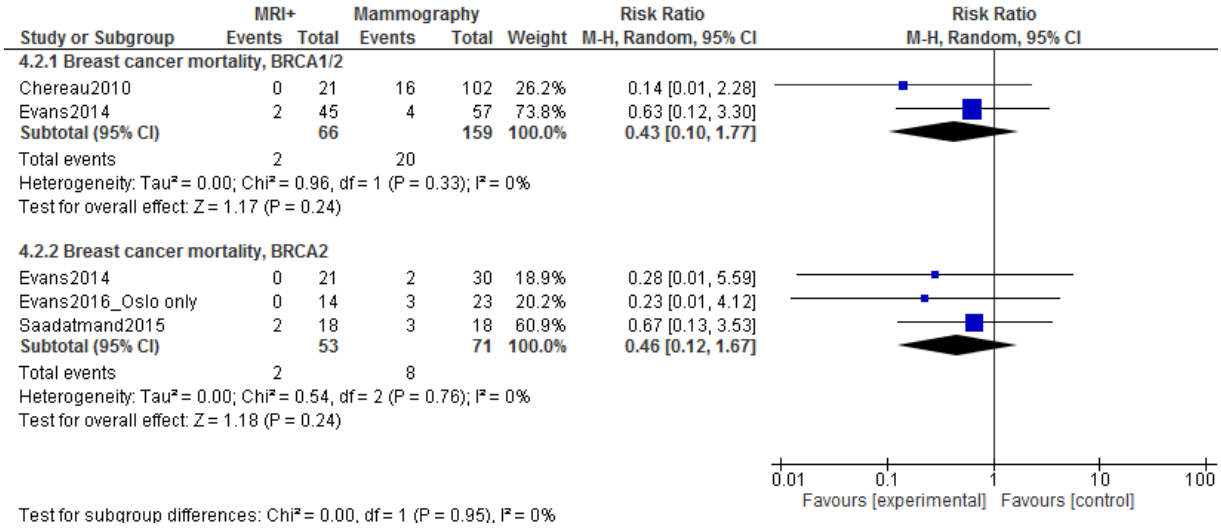


Table 11. *Certainty of evidence of mortality among women with BRCA1/2 mutations: MRI+ compared to mammography*

Patient or population: Women with BRCA1/2 or only BRCA2 mutations
Intervention: MRI and mammography
Comparison: Mammography

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with mammography	Risk with MRI + mammography			
Breast cancer mortality, BRCA1/2	126 per 1 000	54 per 1 000 (13 to 223)	RR 0.43 (0.10 to 1.77)	225 (2 observational studies)	⊕◯◯◯ VERY LOW [a]
Breast cancer mortality, BRCA2	113 per 1 000	52 per 1 000 (14 to 188)	RR 0.40 (0.12 to 1.67)	124 (3 observational studies)	⊕◯◯◯ VERY LOW [a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio
a. Wide confidence interval

Ongoing trials on hereditary breast cancer screening with MRI

A search for ongoing trails on mortality among women with hereditary breast cancer undergoing screening with MRI identified only two studies (*Table 12*). One study was completed in 2015 but no publications were identified either in the ClinicalTrials.gov or in PubMed. It is likely that there are additional ongoing studies that are not registered in the ClinicalTrials.gov database.

Table 12. *Ongoing trials*

Trial	Design	N	Intervention	Period	Country
National Screening in Denmark With MR Versus Mammography and Ultrasound of Women With BRCA1 or BRCA2 Mutations (MR BRCA) NCT00413491	Interventional Study design: Diagnostic,Prospective,Non Randomised,Blinded,Efficacy study. Phase 4.	300	Comparison of MR and mammography	01/2007-06/2015 Finished, but not published. Status unknown.	Denmark
Comparison of Contrast-enhanced Spectral Mammography (CESM) to MRI in Screening High Risk Women for Breast Cancer NCT02275871	Interventional Study design: Diagnostic, Prospective, Single Group Assignment None Masking (Open Label)	220	Comparison of MRI and CESM	11/2014-01/2019 Estimated Study Completion Date: January 2021	US

Budget impact analysis

This chapter presents the potential budget impact of changing the current practice of breast cancer screening for women with BRCA 1 or 2 mutations. As described in the current Norwegian guidelines (20), these women are screened annually with MRI in combination with mammography from the age of 25 until they are 70. In this chapter, we compare this practice with two alternative strategies:

1) Annual screening with mammography only from age 25 to 70, and;
2) A combination of annual MRI and mammography from age 25 to 50, followed by annual mammography alone up to age 70.

Methods and inputs used in the budget impact analysis

Epidemiological inputs

The key epidemiological estimates used in this budget impact analysis were:

1. The total number of women with BRCA 1 or 2 mutations screened with mammography and MRI annually at Norwegian hospitals
2. The sensitivity and specificity of annual mammography or of mammography combined with MRI
3. The risk of cancer in women with a BRCA 1 or 2 mutation.

Number of women with BRCA 1 and 2 mutations screened in Norway each year

We asked the four regional centers for hereditary cancers for the number of women with BRCA 1/2 mutations referred to annual breast cancer screening with mammography and MRI in 2016 from their respective regions. We received answers from three of the four Regional Health Authorities (RHA, South-Eastern Norway, Central Norway, and Western Norway) which are the three largest RHAs. For the Northern Norway RHA, we estimated the number of women aged 25 to 70 in 2016 in the three northern counties using data from Statistics Norway[1] and calculated the number referred in that region assuming that the proportion of referrals was the same as in the Central Norway RHA. The estimated number of women annually re-

[1] Statistisk sentralbyrå, Folkemengde, etter region, kjønn, alder, tid og statistikkvariabel, 2016

ferred in the Northern Norway RHA was 69. The figure from the Western region was also estimated based on that reported for 2014 (320 patients) and an assumed decrease in referrals corresponding to that of Central Norway of approximately 10%. The estimated number of women with genetic mutations referred to breast cancer screening in 2016 was 1,156. This number includes carriers of BRCA1, BRCA2, PTEN, and P53 mutations. We subtracted 2.5% of women who are expected to have another genetic mutation than BRCA 1/2 (personal communication). The estimated total number of women with BRCA1 or BRCA2 mutations referred to screening with MRI and mammography in 2016 in Norway was 1,127. Of these, 45% are expected to have a BRCA2 mutation (personal communication). *Table 13* shows the number of women with BRCA 1 or 2 mutations referred to annual breast cancer screening in the four RHAs.

Table 13. *The number of women referred to annual breast screening using MRI and mammography in 2016*

Regional Health Authority (RHA)	Number of women*
South-Eastern Norway	699
Central Norway	100
Western Norway	288
Northern Norway*	69
Sum all RHA	1156
Correction for other gene mutations**	(-294)
Total	1,127 BRCA1: 620 (55%) BRCA2: 507 (45%)

Numbers for 2017 is not yet available.
*Assuming the same proportion screened as in Central Norway RHA
** Subtracting 2.5% assumed to have another genetic mutation than BRCA 1 or 2

There may be deviations between the number of women referred to for screening, and those who actually attended screening. Furthermore, the number of women referred to annual screening differs from the number of women with BRCA1 or BRCA2 mutations in the population, which is higher. Indeed, not all women are aware of their mutation status, and others may have chosen to conduct risk-reducing surgery rather than attend breast cancer screening.

We did not have any information on either the age-distribution of, or the mean/ median age of the women referred to for screening in 2016. In order to have an estimate of the number of women with BRCA 1/2 mutations in each age group, we used the number of women aged 25 to 70 in Norway on the January 1st 2016 in 5-year age groups (36). To calculate the number of women carrying a BRCA1 or BRCA2 mutation, we used an estimate of BRCA1 and BRCA2 prevalence of 1/397 (1) and assumed equal prevalence rates across age groups. Furthermore, not all women who have BRCA1 and BRCA2 genetic mutations are referred to screening. Based on our estimate of the total number of women referred to screening of 1,127 (*Table 17*), we estimated that about 36% of women with BRCA1 and BRCA2 are referred to screening.

Table 14 summarizes our estimates of the number of women referred to screening for each 5-year age groups, and for BRCA1 and BRCA2 genetic mutations, separately.

Table 14. *Estimated total number of women referred to breast cancer screening*

Age	Total number of women*	Women referred to screening**		
		BRCA 1***	BRCA 2***	Total
25-29	178 175	74	61	135
30-34	169 946	71	58	129
35-39	165 634	69	57	126
40-44	179 503	75	61	136
45-49	182 590	76	62	139
50-54	167 144	70	57	127
55-59	156 037	65	53	119
60-64	144 666	60	49	110
65-69	139 857	58	48	106
Total	1 483 552	620	507	1 127

* Women alive on 01.01.2016 in Norway. Source: Statistics Norway

** Based on the estimate that about 36% of those with prevalent BRCA 1/2 are referred to screening. Numbers are rounded so the total might differ slightly from the sum of the BRCA1 and BRCA2 columns.

*** Based on a prevalence of BRCA 1/2 of 0.25% (1/397) (37). Numbers based on the proportion: BRCA 1 (55%) and BRCA 2 (45%) of the total.

The sensitivity and specificity of the different screening strategies

We used sensitivity and specificity estimates from an individual patient data meta-analysis that compared annual mammography with annual mammography in combination with MRI (MRI+) in a BRCA1 and BRCA2 population (30). These estimates are presented in *Table 15*. As sensitivity is higher for the combination strategy and specificity is lower, it can be expected that the MRI+ result in more screening-detected cancers, but at the expense of more false positive results.

Table 15. *Sensitivity and specificity for BRCA1 and BRCA2 used in our calculations*

Mutation	Age	Mammography		MRI+	
		Sensitivity	Specificity	Sensitivity	Specificity
BRCA1	30-40	0,39	0,95	0,87	0,81
	40-50	0,34	0,92	0,94	0,77
	50-60	0,29	0,97	0,89	0,87
	60-70	0,29	0,97	0,89	0,87
BRCA2	30-40	0,56	0,92	0,87	0,75
	40-50	0,38	0,92	0,91	0,8
	50-60	0,46	0,97	0,94	0,89
	60-70	0,46	0,97	0,94	0,89

Source (both sensitivity and specificity): Phi et al 2016 (38)

The risk of breast cancer in women carrying a BRCA1 or BRCA2 genetic mutation

The annual incidence of breast cancer in a Norwegian BRCA 1 population has been estimated by Møller et al. (39). *Table 16* presents these estimates, and shows that the incidence increases with age and peaks at around age 50 to 59. We are not aware of any similar estimates for the BRCA 2 population in Norway, and therefore applied the BRCA 1 rates to the BRCA 2 population.

Table 16. *Age specific incidence rates for breast cancer in carriers of BRCA1 mutations by age from the publication by Møller et al. (39)*

Age	BRCA 1 (%)
30-34	1.9
35-39	1.9
40-44	2.2
45-49	2.2
50-54	3.1
55-59	3.1
60-64	1.1
65-69	1.1

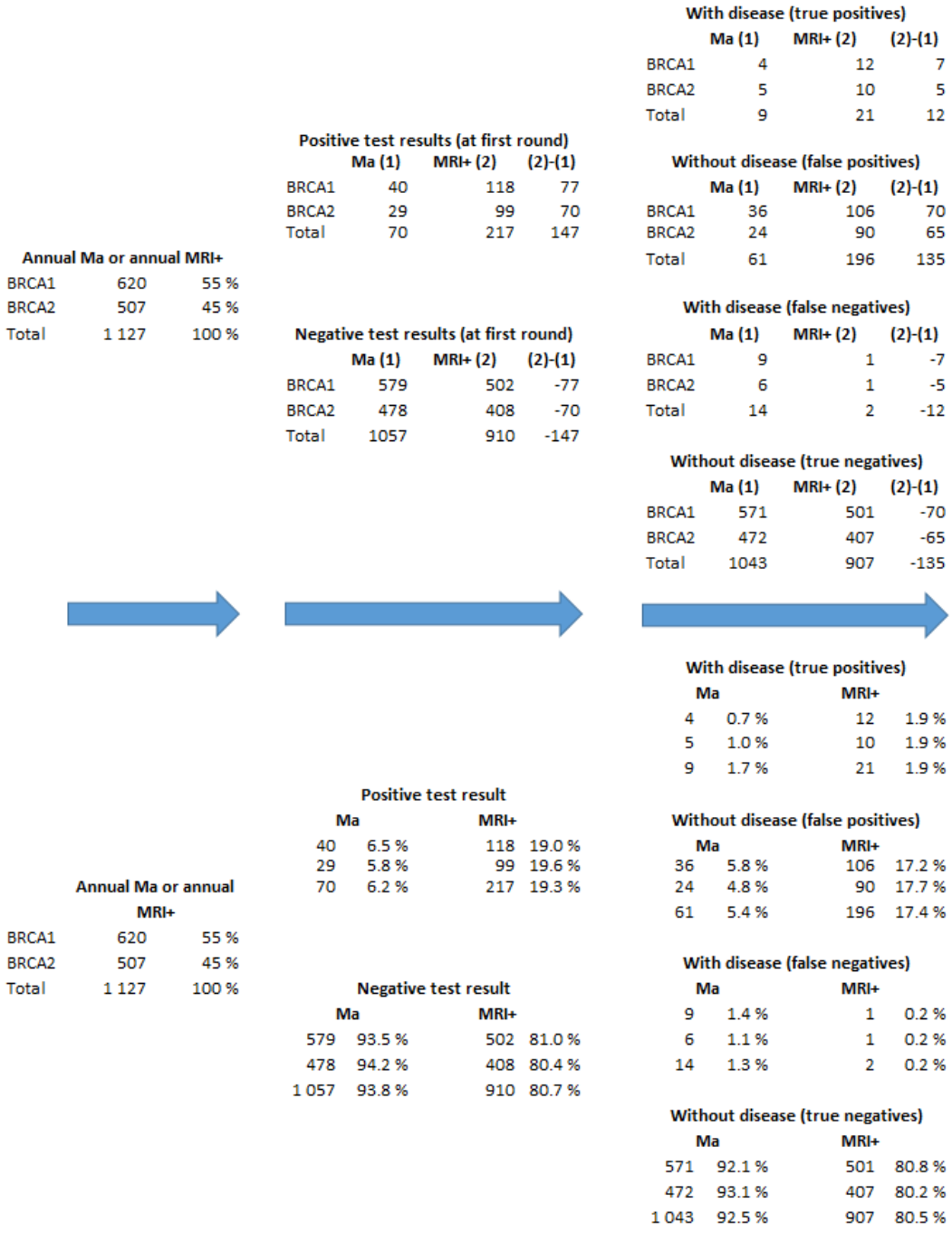
True, false positive and false negative tests for different screening strategies

We calculated the number of true and false positive and negative test results for each screening strategy. For that, we used estimates of sensitivity, specificity and risk of disease (38). Considering the number of women with BRCA1 or BRCA2 mutations referred to breast cancer screening in 2016 as the number of women screened, we estimated the number of positive and negative results for each strategy. Finally, we calculated the number of true and false positive and negative tests for each strategy. We estimated these numbers comparing annual mammography alone from age 25 to 70 to:

1) Annual mammography and MRI from age 25 to 70 (results are presented in *Figure 7*)
2) Annual mammography and MRI from age 25 to 50 followed by mammography alone until age 70 (results are presented in *Figure 8*).

As shown in *Figure 7*, changing current practice (annual mammography and MRI from age 25 to 70) to a strategy with annual mammography alone from age 25 to 70, will result in approximately 147 fewer positive tests (first round), representing 12 fewer true positives breast cancers and 135 fewer false positive findings for BRCA1 and BRCA2 combined.

Figure 7. *Breast cancer screening tests results of mammography in combination with MRI (MRI+) from age 25-70 and mammography alone (Ma) from age 25 to 70.*



The alternative scenario examined was to offer MRI only for women with BRCA1 and BRCA2 genetic mutation aged under 50, that is, annual mammography and MRI from age 25 to 50 and only mammography to age 70 (*Figure 8*). Such a screening strategy would roughly correspond to the recommendation of the National Institute for Health and Care Excellence (NICE) (24). We estimated that adopting this screening strategy would result in approximately 47 fewer positive screening results (first round), 5 fewer screening detected cancers and 41 fewer false positive findings (BRCA 1 and 2 combined), compared to current practice.

Figure 8. *Breast cancer screening tests results of mammography (Ma) from age 25-70 and mammography in combination with MRI (MRI+) from age 25 to 50, followed by mammography alone until age 70*

Annual Ma or annual MRI+

BRCA1	620	1
BRCA2	507	0
Total	1127	1

Positive test results (at first round)

	Ma (1)	MRI+ (2)	(2)-(1)
BRCA1	90	118	50
BRCA2	81	99	18
Total	171	217	47

Negative test results (at first round)

	Ma (1)	MRI+ (2)	(2)-(1)
BRCA1	530	502	-28
BRCA2	426	408	-18
Total	956	910	-89

With disease (true positives)

	Ma (1)	MRI+ (2)	(2)-(1)
BRCA1	8	12	3
BRCA2	7	10	2
Total	16	21	5

Without disease (false positives)

	Ma (1)	MRI+ (2)	(2)-(1)
BRCA1	81	106	25
BRCA2	73	90	16
Total	155	196	41

With disease (false negatives)

	Ma (1)	MRI+ (2)	(2)-(1)
BRCA1	5	1	-3
BRCA2	3	1	-2
Total	8	2	-5

Without disease (true negatives)

	Ma (1)	MRI+ (2)	(2)-(1)
BRCA1	525	501	-25
BRCA2	423	407	-16
Total	948	907	-41

Economic inputs

The budgetary consequences outlined here are limited to the first round of screening and the expenses of confirming positive results. We did not consider expenses related to treatment following the detection of cancer. All of the expenses are expressed in 2016 Norwegian kroner (NOK), and include depreciation and overhead expenses. We consider a time-perspective of 1 year for each screening program.

We received relevant hospital expenses from Oslo University Hospital (personal communication). The hospital expenses associated with each breast MRI are approximately 5,000 NOK including depreciation and overhead. The hospital expenses used in the budget impact calculations are shown in *Table 17*. When breast cancer screening is conducted with the MRI+ (MRI and mammography), a limited mammography is always conducted (20). This limited mammography is slightly less resource intensive than a full mammography. The expenses for examinations following a positive finding consist of a mix of cytology, needle biopsy and vacuum biopsy in combination with ultrasound. Alternatively, the patient is referred to a follow-up MRI and mammography (personal communication).

According to the patient co-payment regulations for outpatient health services for radiological examinations (40) the out-of-pocket payment is 245 NOK. Therefore, this amount was subtracted from the cost to the hospital in the budget impact analysis.

Table 17. *Hospital expenses associated with mammography, MRI and limited mammography, and with the examination following a positive finding on the initial screen*

Type of diagnostic service	Hospital expenses (NOK)
Mammography	2,200
MRI and limited mammography	6,950
Examination following positive finding (Biopsy/ultrasound or MRI and limited mammography)	6,258

Results of the budget impact analysis

The results for BRCA 1 and 2 mutations separately, and for both combined, are shown for the following three strategies:

1. The current practice using annual mammography and MRI from age 25 to 70
2. The alternative scenario of annual mammography and MRI from age 25 to 50 followed by annual mammography to age 70
3. Annual mammography alone from age 25 to 70

Table 18 shows the expenses for the three above-mentioned strategies. For all strategies, the highest expenses are related to initial screening (and less to follow-up of a positive test). The initial screening costs exceeds the expenses of confirming positive tests approximately fivefold.

The strategy that involves annual mammography and MRI from age 25 to 50 followed by annual mammography alone to age 70 (strategy 2) saves approximately 1.4 million NOK per year for BRCA 1 and 1.1 million NOK for BRCA 2 annually compared to the current practice (strategy 1). The combined annual saving of approximately 2.4 million NOK results in approximately 12 million NOK saved over a 5-year horizon.

The strategy that involves mammography alone (strategy 3) saves approximately 6.2 million NOK annually, with savings of 3.4 million NOK for BRCA 1, and 2.8 million NOK for BRCA 2, compared to the current practice (strategy 1). Over a 5-year horizon, the cumulative combined annual saving is approximately 31 million NOK.

Table 18. *Annual expenses associated with three screening strategies broken down to the expenses of the initial screening, and the expenses related to confirming positive tests*

BRCA 1	1.MRI+	2.MRI+<50	3.Ma	(1)-(2)	(1)-(3)
Initial screening	4 155 315	2 949 480	1 211 580	1 205 836	2 943 736
Positive test	708 840	539 671	243 198	169 169	465 642
Total cost(NOK)	4 864 155	3 489 151	1 454 777	1 375 005	3 409 378
BRCA 2	1.MRI+	2.MRI+<50	3.Ma	(1)-(2)	(1)-(3)
Initial screening	3 399 803	2 413 211	991 292	986 593	2 408 511
Positive test	596 696	485 967	176 564	110 729	420 132
Total cost (NOK)	3 996 500	2 899 178	1 167 856	1 097 322	2 828 643
BRCA 1&2	1.MRI+	2.MRI+<50	3.Ma	(1)-(2)	(1)-(3)
Initial screening	7 555 119	5 362 690	2 202 872	2 192 499	5 352 247
Positive test	1 305 536	1 025 638	440 949	279 898	885 775
Total cost (NOK)	8 860 655	6 388 329	2 622 634	2 472 326	6 238 021

MRI+, MRI (magnetic resonance imaging) and mammography; Ma, Mammography; BRCA1/2, Women with BRCA 1 or 2 gene mutation.

The inputs with the greatest influence in the budget impact analysis were: MRI screening costs, the number of screened women, the cost of confirming positive findings, and the screening performance (sensitivity and specificity).

Discussion

Summary of results

The current screening strategy in Norway for women with BRCA1 and BRCA2 mutations is annual MRI and mammography from the age of 25 to 70.

In this HTA, we have systematically reviewed and summarized studies on

- diagnostic accuracy of MRI and mammography, and the two combined, for detection of breast cancers, and
- effectiveness of MRI and mammography as a combined screening program for reduction of mortality in women with HBOC, with subgroup analyzes of BRCA1 and BRCA2 mutation carriers

In addition, we have performed a budget impact analysis for two alternative screening strategies.

Clinical outcomes

- MRI is much more sensitive than mammography while mammography is more specific than MRI. By combining the two modalities, more true positive breast cancer cases would be identified but also more false positive cases.
- We were not able to detect a difference in breast cancer mortality or overall cancer mortality among women at high risk for breast cancer following either an annual MRI and mammography-screening program or an annual mammography-only-screening. The certainty of the evidence is too low to allow strong conclusions.
- We have not performed any safety analyses of the different screening programs, for example potential risks of radiation-induced cancer by mammography in young women.
- We did not have data to perform analyzes on effectiveness of different screening programs based on age.

Economical outcomes

- If MRI is removed from the current screening program to women with BRCA1 and BRCA2 mutations, annual savings compared to current practice will be 6.2 million NOK. Over a 5-year horizon, the cumulative combined annual saving is approximately 31 million NOK.
- If MRI is offered in combination with mammography to women with BRCA1 and BRCA2 mutations from age 25 to 50, followed by only mammography up to the age of 70, annual

savings compared to current practice will be 2.5 million NOK. Over a 5-year horizon, the cumulative combined annual saving is approximately 12 million NOK.

Discussion of clinical outcomes

Breast cancer in BRCA1 mutation carriers are associated with more aggressive tumor characteristics compared to BRCA2 and are also less visible on mammography (41). Furthermore, MRI have shown to be more sensitive than mammography while mammography is more specific than MRI. A combination of the two will increase the sensitivity but would lower the specificity (38). By combining the two, more true positive breast cancer cases will be identified, but also more false positive cases.

The ideal way to investigate the effectiveness of screening interventions for detection of breast cancers is prospective studies starting when women are identified with a high risk of breast cancer through family history, and to follow them until breast cancer development or other clinical endpoints of interest. In our evaluation, only one study used such a method (32;33).

An alternative approach for studying effectiveness of screening interventions, is to recruit women with breast cancer diagnosis and who are identified as women with high risk of breast cancer, and divide them in groups depending on the screening regimen they had been following up to that date. Two studies used this approach (31;34).

In the identified studies, control groups were defined differently and performing meta-analyses was therefore challenging. However, we extracted data from three different screening groups and compared the survival of women between these groups: 1) MRI and mammography, 2) mammography alone or 3) no or less intensive screening. Data on overall cancer mortality and breast cancer mortality were presented for both women with HBOC and for BRCA1 and BRCA2 mutation carriers specifically.

The studies by Evans et al (32;33) were the only ones that followed asymptomatic women from initiation of a screening regimen up to breast cancer diagnosis. Comparing breast cancer mortality among women enrolled in an MRI and mammography screening program with breast cancer mortality among those who followed a screening program involving mammography only, non-statistically significant lower breast cancer mortality was observed. For these data sets, the confidence intervals are influenced by the very low number of events (below 1%). Thus, the results have very low certainty.

For the studies following their study subjects from cancer diagnosis (31;34), a non-statistically significant lower breast cancer mortality rate was observed if BRCA1/2 mutations carriers were screened with both MRI and mammography compared to mammography alone. This non-statistically significant lower breast cancer mortality was also noted among HBOC and BRCA2 populations. As above, the low number of events (below 1%) gives results with very low certainty.

To improve early detection of breast cancer with the ultimate goal to increase survival rate, several countries have introduced MRI in addition to mammography as a screening regimen for high-risk women. These recommendations seem to be based on the higher sensitivity of MRI over mammography (42;43). We found only four studies addressing the benefit of introducing MRI on breast cancer survival (31-34). The MARIBS study is the largest clinical study in Europe that have investigated the role of MRI in high-risk breast cancer women (44). However, there is still an uncertain evidence-based rational for introducing MRI at an early age in high-risk breast cancer women based on beneficial breast cancer survival. One study used a computer simulation model to compare six annual screening strategies (based on different modalities and age) and concluded that annual MRI at age 25 and delayed alternating digital mammography at age 30 is likely to be the most effective screening strategy in BRCA mutation carriers (45). Screening benefits, associated risks and personal acceptance of false-positive results, should be considered in choosing the optimal screening strategy for individual women (45).

Introducing intensive screening regimen from the age of 25 years introduces a potential risk of radiation-induced breast cancer in young women carrying mutations. Obdeijn et al (46) propose to screen women with BRCA1 mutations yearly with only MRI from age 25 onwards and to start with mammographic screening not earlier than age 40 and conclude that there was no benefit of additional mammography in women below age 40. Two small studies of BRCA mutations found no association between mammogram exposure and breast cancer risk (47;48). Others studies show that the incidence of breast and ovarian cancer in BRCA2 mutation carriers and of ovarian cancer in BRCA1 mutation carriers is still high after 60 years (49) and should therefore justify intensive breast screening as well as oophorectomy even after age 60. The risk of contralateral breast cancer rises approximately 3% per year, which may affect preventive choices (49).

Many young women are not aware of their mutation status even if they have family history of breast cancer. An accurate estimate of lifetime risk of breast and ovarian cancer are crucial for counselling women from BRCA1/2 families. This is dependent on the penetrance of their mutations; many mutations are well known as pathogenic. Risk assessment and counselling are based on published penetrance estimates of breast and ovarian cancers that show varying results worldwide (50). The observed increase in screening in BRCA1/2 carriers is consistent with the high risk of developing breast cancer in this group. The estimation of the cancer risk associated with an inconclusive result is often based on familial cancer history, and women who received this result appear to have received follow-up as if at high risk (51). While breast MRI surveillance did not have a detrimental psychological impact on women with a BRCA1 or BRCA2 mutation, recalling these very high-risk women for further imaging after a false positive MRI scan temporarily increased their anxiety (52-54).

In this report, we have not considered potential detrimental effects of radiation due to the screening strategies. Also, we have not discussed the effect of breast cancer treatment after diagnoses on mortality rate. Further, we did not have data to perform analyzes on effectiveness of different screening programs based on age.

Discussion of the budget impact

As one would expect, less resource-intensive screening strategies may result in less screening-detected cancers, but also fewer false positive findings. The former consequence is clearly negative if one assumes a benefit from more screening detected cancers. The latter consequence is positive if one considers the associated resource consumption and possible anxiety related to false positive findings.

The budget impact analysis shows the order of magnitude of the budgetary savings if less resource-intensive screening strategies are chosen. The usefulness of the results may, however, be criticized for a number of reasons.

First of all, the input data we used may be incomplete both with respect to the number of women screened and age-specific cancer incidence. The screening test performance data were, on the other hand, valid for BRCA1 and BRCA2 population separately for each subpopulation. Lastly, we did not know the age distribution of the BRCA1/2 population that are referred to screening. Because of these limitations, the calculations should be handled with caution even if we have differentiated between the BRCA 1 and 2 populations with regard to the number of positive screening tests and false positive test results.

Secondly, the budget impact analysis did not include any consequences of different screening strategies for resource use for further treatment. If it is more expensive to treat cancers with a less favorable stage distribution, as have been shown by others (55), this would favor the current practice of annual MRI screening.

Thirdly, a budget impact analysis does not capture the impact of different strategies on survival, quality adjusted life years and costs, in a life-time perspective. It only highlights the potential expenses that the hospital could save in a hypothetical situation where the reduced MRI activity is not replaced by other MRI activity. Since MRI is a scarce resource, we have reason to believe that any MRI spare capacity could be used for other activities, hence there is a limited potential for budgetary savings per se. In order to provide information about potential areas of disinvestment in MRI capacity, one should rather conduct a cost-effectiveness analysis that also includes other MRI uses. However, a cost-effectiveness analysis of different breast cancer screening strategies in the Norwegian context could still be of relevance to decision makers if the aim is to determine which strategy to recommend in clinical practice.

Other studies have conducted cost-effectiveness analyses. The authors' conclusions regarding cost-effectiveness of the screening strategy that involved MRI and mammography ranged from no clear conclusion regarding cost-effectiveness (56;57) to 'potentially cost-effective' (58) to 'likely cost-effective' (59;60) to 'cost-effective' (61). The costs related to retesting positive breast cancer screening results is included in other studies. This is an important cost to include because MRI screening is expected to result in higher false positive screening results compared to mam-

mography. However, the potential for over diagnosis and associated costs was typically not included because of limited information on these parameters (58;59). In this setting, over diagnosis means detection of cancers that would not have threatened survival. A further limitation of the costs data in the included studies is that MRI costs were often derived from tariffs. Costs that are estimated based on tariffs may not reflect the actual cost of the service (i.e., actual costs may be underestimated or overestimated).

The recommendation of NICE (24) is to offer annual MRI surveillance to women aged 30–49 years with a known BRCA1 or BRCA2 mutation. The recommendation from NICE is not to offer MRI to women at the aged 50–69 years with a known BRCA1 or BRCA2 mutation, unless mammography has shown a dense breast pattern.
Cancer care Ontario in Canada conclude that while there is insufficient evidence at this time to make a definitive recommendation regarding the ages of patients who should be screened, it is the opinion that women should be screened annually from 30 to 69 years of age (62).

Breast MRI has advantages over other techniques (panel) in its ability to image cancer with excellent sensitivity without the use of ionizing radiation, and to image the radiographically dense breast (i.e., young women or those on hormone-replacement therapy). Other potential uses in which breast MRI may have an advantage are in the detection or exclusion of recurrence after breast-conserving surgery, the assessment of cancer in the presence of implants, the detection of multifocal disease, the investigation of women with large axillary nodes of unknown cause, and the monitoring of neoadjuvant chemotherapy. The disadvantages are cost, inability of some patients to tolerate the enclosed space, lack of availability, time needed to carry out the procedure, substantial differences in reported specificities, and lack of established biopsy procedures for lesions not found on mammography or ultrasound.

Newer imaging techniques have emerged over the last few years such as tomosynthesis, contrast enhanced spectrum mammography and automated whole breast ultrasound (63-65). Yet, there is still insufficient data on these new techniques to justify changing current practices.

Conclusion

Changing current practice for breast cancer screening in women with BRCA1/2 mutation from annual MRI and mammography to only mammography, gives less false positive, but also less true positive, detections. The budget impact model, shows an annual saving of 6.2 million NOK. The model used includes follow-up diagnostics (biopsy and ultrasound) for all test positive cases.

Adding MRI to an annual mammography-screening program has not shown to statistically significant reduce breast cancer mortality among women with HROC generally, or BRCA1/2 mutations specifically, compared to mammography screening alone.

Alternative screening regimen of offering annual MRI and mammography to women between 25 and 50 years, followed by mammography only from 50-70 years, have not been analyzed with regard to effectiveness as no age-specific data on mortality were available. However, the budget impact analyses showed and annual saving of 2.5 million NOK for this alternative based on the screening costs.

Need for further research

The challenge in reviewing the evidence for the effectiveness of MRI screening is the lack of randomized trials. Once preliminary evidence from comparative pilot studies of MRI and mammography was available, randomized studies were no longer considered to be feasible, and perhaps not even ethical. In addition, the follow-up in the published comparative studies discussed in this review is still too short for recurrence and survival data to be available for women with MRI-detected cancers. Future studies should have longer follow-up and report the association between screening detected breast cancers, stage distribution at diagnosis and treatment costs. In addition, the impact of different breast cancer screening strategies on health-related quality of life should been investigated. Potential risk of radiation-induced breast cancer is highly relevant when choosing a screening modality for identifying breast cancers, in particular in young women carrying a mutation. However, we have not considered this in the present report and more studies will be needed to assess this risk.

Implications for practice

MRI capacity is a scarce resource for hospitals and MRI capacity used for breast cancer screening of BRCA 1/2 carriers could, for example, be substituted with MRI activities aimed at other patient populations.

This report shows that the current practice probably detects more false positive breast cancers than if a reduced use of MRI in the screening programs were implemented. However, this report has not considered whether the reduction of true positive breast cancers would threaten survival. While the significantly greater sensitivity of MRI is unquestionable, its ultimate clinical effectiveness depends on its ability to reduce mortality. This health technology assessment cannot conclude on survival data for women with mammography or MRI-detected cancers.

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Appendix

Appendix 1. Search Strategy

Literature search for MRI screening in women with BRCA mutations

Date run: 2015.04.16 and 2016.01.25

Databases: Ovid MEDLINE, Embase (Ovid); Cochrane Library; Centre for Reviews and Dissemination: Database of Abstracts of Reviews of Effects , Health Technology Assessment Database, NHS Economic Evaluation Database; Web of Science; PubMed (epub ahead of print)

Sources: WHO International Clinical Trials Registry Platform, ClinicalTrials.gov

Search filter: Ovid filter "reviews (maximizes specificity)" and text words (systematic* adj2 (review* or overview)); "therapy (maximizes specificity)"; Cochrane EPOC-filter

Year limit: 2010-2016

Total results: 1020

Searched by: Ingrid Harboe, peer reviewed by Elisabet Hafstad, information specialists

Search strategies

Databases: Embase 1974 to 2016 Week 04
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	Genes, BRCA1/ use pmez [ex code pmoz]	5040
2	Genes, BRCA2/ use pmez	3069
3	tumor suppressor gene/ use oemez	51122
4	((Breast cancer* or breast neoplasm* or breast tumo*r*) adj4 gene*).tw.	24025
5	("BRCA1" or "BRCA 1").tw.	24837
6	("BRCA2" or "BRCA 2").tw.	13421
7	or/1-6	95519
8	exp Magnetic Resonance Imaging/	976898
9	(Magnetic Resonance Imag* or MRI or "MR imag*").tw.	690648
10	Mammography/	65081
11	mammograph*.tw.	53408
12	exp Mastectomy/	68713
13	(Mastectomy or Mastectomies or Mammectomy or Mammectomies).tw.	40828

14	Ovariectomy/	52986
15	(Ovariectomy or Ovariectomies or Oophorectomy or Oophorectomies).tw.	36485
16	or/8-15	1314918
17	7 and 16	5636
18	remove duplicates from 17	4139
19	limit 18 to "reviews (maximizes specificity)"	57
20	(systematic* adj2 (review* or overview)).tw.	184240
21	18 and 20	46
22	19 or 21 [SR]	70
23	22 use oemez	56
24	22 use pmez	14
25	randomized controlled trial/ [epoc-filter Embase]	797550
26	Controlled Clinical Trial/	481511
27	Cohort Studies/	339677
28	Quasi Experimental Study/	2768
29	Pretest Posttest Control Group Design/	248
30	Time Series Analysis/	16394
31	Experimental Design/	98447
32	Multicenter Study/	323555
33	(randomis* or randomiz* or randomly or random allocat*).ti,ab.	1485449
34	(trial or multicentre or multicenter or multi centre or multi center).ti.	404879
35	(prospective adj2 (stud* or trial* or analys*)).tw.	585972
36	(cohort adj2 (stud* or trial* or analys*)).tw.	305046
37	(intervention* or controlled or control group or compare or compared or quasiex-periment* or quasi experiment* or time series or time point? or repeated measur*).ti,ab.	8798471
38	or/25-37	10259933
39	(systematic review or literature review).ti.	152763
40	"cochrane database of systematic reviews".jn.	15429
41	Nonhuman/	4669048
42	or/39-41	4834932
43	38 not 42	9264731
44	43 and 17	2030
45	randomized controlled trial.pt. [epoc-filter Medline]	404579
46	controlled clinical trial.pt.	90003
47	multicenter study.pt.	192312
48	Cohort Studies/	339677
49	(randomis* or randomiz* or randomly allocat* or random allocat*).ti,ab.	1066022
50	groups.ab.	3516238

51	(trial or multicenter or multi center or multicentre or multi centre).ti.	404879
52	(prospective adj2 (stud* or trial* or analys*)).tw.	585972
53	(cohort adj2 (stud* or trial* or analys*)).tw.	305046
54	(intervention* or controlled or control group or compare or compared or quasiex-periment* or quasi experiment* or time series or time point? or repeated measur*).ti,ab.	8798471
55	or/45-54	11468523
56	exp Animals/	40805754
57	Humans/	27548266
58	56 not (56 and 57)	13260676
59	review.pt.	4176135
60	meta analysis.pt.	60556
61	news.pt.	173752
62	comment.pt.	648442
63	editorial.pt.	889924
64	cochrane database of systematic reviews.jn.	15429
65	comment on.cm.	648442
66	(systematic review or literature review).ti.	152763
67	or/58-66	18201745
68	55 not 67 [EPOC MEDLINE]	7221451
69	68 and 17	1347
70	44 or 69	2137
71	limit 17 to "therapy (maximizes specificity)"	88
72	70 or 71	2144
73	limit 72 to yr="2010 -Current"	1131
74	73 not 22 [not SR from first search]	1114
75	remove duplicates from 74	858
76	limit 22 to yr="2015 -Current" [SR filter update search]	13
77	limit 73 to yr="2015 -Current" [clinical trials update search]	182
78	remove duplicates from 77	140

Database: Cochrane Libary

Date Run: 15/04/15 and 2016/01/25

Results: 62

ID	Search	Hits
#1	MeSH descriptor: [Genes, BRCA1] explode all trees	83
#2	MeSH descriptor: [Genes, BRCA2] explode all trees	63
#3	((Breast cancer* or breast neoplasm* or breast tumo*r*) near/4 gene*):ti,ab,kw	506
#4	(BRCA1 or BRCA 1):ti,ab,kw	305
#5	(BRCA2 or BRCA 2):ti,ab,kw	227
#6	#1 or #2 or #3 or #4 or #5	729
#7	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	5924
#8	(Magnetic Resonance Imag* or MRI):ti,ab,kw	12277

#9	MeSH descriptor: [Mammography] explode all trees	967
#10	mammograph*:ti,ab,kw	1653
#11	MeSH descriptor: [Mastectomy] explode all trees	1336
#12	(Mastectomy or Mastectomies or Mammectomy or Mammectomies):ti,ab,kw	2595
#13	MeSH descriptor: [Ovariectomy] explode all trees	287
#14	(Ovariectom* or Oophorectom*):ti,ab,kw	725
#15	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	17101
#16	#6 and #15 Publication Year from 2010 to 2015	58
#17	#16 Publication Year from 2015 to 2016	4

Database: PubMed

Date: 2015.04.16 and 2016/01/25
Results: 27
Search:
(("2015/01/01"[Date - Publication] : "3000"[Date - Publication]))
AND ((((publisher [sb]) OR pubstatusaheadofprint))
AND
(((((((Genes, BRCA1[MeSH Major Topic]) OR Genes, BRCA2[MeSH Major Topic]) OR (("Breast cancer* gene*"[Title/Abstract] OR "breast neoplasm* gene*"[Title/Abstract] OR "breast tumo*r* gene*"[Title/Abstract]))) OR (("BRCA1"[Title/Abstract] OR "BRCA 1"[Title/Abstract]))) OR (("BRCA2"[Title/Abstract] OR "BRCA 2"[Title/Abstract])))))
AND
(((((((Magnetic Resonance Imaging[MeSH Major Topic]) OR (("Magnetic Resonance Imag*"[Title/Abstract] OR MRI[Title/Abstract] OR "MR imag*"[Title/Abstract]))) OR Mammography[MeSH Major Topic]) OR mammograph*[Title/Abstract]) OR Mastectomy[MeSH Major Topic]) OR ((Mastectomy[Title/Abstract] OR Mastectomies[Title/Abstract] OR Mammectomy[Title/Abstract] OR Mammectomies[Title/Abstract]))) OR Ovariectomy[MeSH Major Topic]) OR ((Ovariectomy[Title/Abstract] OR Ovariectomies[Title/Abstract] OR Oophorectomy[Title/Abstract] OR Oophorectomies[Title/Abstract])))))))

Database: Web of Science

Date: 2015.01.28 and 2016.01.25
Results: 60 SR/ HTA

# 8	#6 AND #3 Refined by: Databases: (WOS) AND DOCUMENT TYPES: (REVIEW OR ARTICLE OR ABSTRACT) Timespan=All years Search language=Auto
# 7	#6 AND #3 Timespan=All years Search language=Auto
# 6	TOPIC: ("systematic* review*") OR TOPIC: ("health technology assessment" or HTA) Timespan=All years Search language=Auto
# 5	TOPIC: (systematic* review*) Timespan=All years Search language=Auto
# 4	TOPIC: (BRCA1 or "BRCA 1" or "Breast cancer gene*") OR TOPIC: (BRCA2 or "BRCA 2") AND TOPIC: (Magnetic Resonance Imag* or MRI or "MR imag*" or mammograph* or Mastectomy or Mastectomies or Mammectomy or Mammectomies or Ovariectomy or Ovariectomies or Oophorectomy or Oophorectomies) Refined by: DOCUMENT TYPES: (REVIEW)

Timespan=All years
Search language=Auto

# 3 TOPIC: (BRCA1 or "BRCA 1" or "Breast cancer gene*") OR TOPIC: (BRCA2 or "BRCA 2") AND TOPIC: (Magnetic Resonance Imag* or MRI or "MR imag*" or mammograph* or Mastectomy or Mastectomies or Mammectomy or Mammectomies or Ovariectomy or Ovariectomies or Oophorectomy or Oophorectomies)
Timespan=All years
Search language=Auto

# 2 TOPIC: (BRCA1 or "BRCA 1" or "Breast cancer gene*") OR TOPIC: (BRCA2 or "BRCA 2")
Timespan=All years
Search language=Auto

# 1 TOPIC: (BRCA1 or "BRCA 1" or "Breast cancer gene*")
Timespan=All years
Search language=Auto

Search for ongoing trials:

Source: WHO International Clinical Trials Registry Platform

Search: breast cancer AND brca AND mri

Results: 2

Recruitment status	Prospective Registration	Main ID	Public Title	Date of Registration
Not recruiting	Yes	ACTRN12617000679381	Magnet Resonance to Manage Breast Disease	12/05/2017
Not recruiting	Yes	NCT01257152	Screening MRI for Cancer Recurrence in Patients Treated With Breast Conserving Therapy	08/12/2010

Appendix 2. Evaluation of full text primary studies

One study was added after the regular search (#27).
Abbreviations: Y=yes, N=No, U=Unknown

Study	P	I	C	O	S	Inclusion / Exclusion
1. Banks AL, Titus R, Melnik M. Detection of new or additional significant breast disease by MRI compared to standard imaging in "high-risk" and "non-high-risk" patients. J Clin Oncol 2013;1).				N		Excluded (meeting abstract)
2. Bosse K, Graeser M, Gossmann A, Hackenbroch M, Schmutzler RK, Rhiem K. Supplemental screening ultrasound increases cancer detection yield in BRCA1 and BRCA2 mutation carriers. Arch Gynecol Obstet 2014;289(3):663-670.	Y	N	N	N	Y	Excluded (ultrasound is part of the intervention)
3. 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. Clin Breast Cancer 2010;10(2):113-118.	**Y**	**Y**	**Y**	**Y**	**Y**	**Included** **(ultrasound is part of the intervention and control group)**
4. Chiarelli AM, Prummel MV, Muradali D, Majpruz V, Horgan M, Carroll JC, et al. Effectiveness of screening with annual magnetic resonance imaging and mammography: Results of the initial screen from the Ontario High Risk Breast Screening Program. J Clin Oncol 2014;32(21):2224-2230.	Y	Y	N	N	N	Excluded
5. Duffy SW, Mackay J, Thomas S, Anderson E, Chen TH, Ellis I, et al. Evaluation of mammographic surveillance services in women aged 40-49 years with a moderate family history of breast cancer: a single-arm cohort study. Health technology assessment (Winchester, England) 2013;17(11):vii-xiv, 1-95.	Y	Y	N	N	N	Excluded (Use of a model to predict mortality)
6. Ehsani S, Strigel R, Pettke E, Wilke L, Szalkucki L, Tevaarwerk AJ, et al. Screening magnetic resonance imaging (MRI) of the breast in				N		Excluded (meeting abstract)

Study	P	I	C	O	S	Inclusion / Exclusion
women at increased lifetime risk for breast cancer: A retrospective single institution study. Cancer Res 2012;3).						
7. Elmore L, Margenthaler JA. The use of breast MRI surveillance in women at high risk for breast cancer: A single institutional experience. Ann Surg Oncol 2010;17:S171.	N	Y	N	N	N	Excluded (Population=Patients undergoing MRI surveillance)
8. Evans DG, Kesavan N, Lim Y, Gadde S, Hurley E, Massat NJ, et al. MRI breast screening in high-risk women: cancer detection and survival analysis.[Erratum appears in Breast Cancer Res Treat. 2014 Oct;147(3):689 Breast Cancer Res Treat 2014;145(3):663-672.	**Y**	**Y**	**Y**	**Y**	**Y**	**Included**
9. Giannakeas V, Lubinski J, Gronwald J, Moller P, Armel S, Lynch HT, et al. Mammography screening and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers: A prospective study. Breast Cancer Res Treat 2014;147(1):113-118.	Y	N	Y	N	Y/N	Excluded (Intervention= mammography Study design= a big component of the study design is restrospective)
10. Heijnsdijk EAM, Warner E, Gilbert FJ, Tilanus-Linthorst MMA, Evans G, Causer PA, et al. Differences in natural history between breast cancers in BRCA1 and BRCA2 mutation carriers and effects of MRI Screening-MRISC, MARIBS, and Canadian studies combined. Cancer Epidemiology Biomarkers and Prevention 2012;21(9):1458-1468.	Y	U	U	Y	N	Excluded (Use of model to ascertain outcomes of interest to us)
11. Le-Petross HT, Whitman GJ, Atchley DP, Yuan Y, Gutierrez-Barrera A, Hortobagyi GN, et al. Effectiveness of alternating mammography and magnetic resonance imaging for screening women with deleterious BRCA mutations at high risk of breast cancer. Cancer 2011;117(17):3900-3907.	Y	N	N	N	N	Excluded
12. Maurice A, Evans DG, Affen J, Greenhalgh R, Duffy SW, Howell A. Surveillance of women at increased risk of breast cancer using mammography and clinical breast examination: Further evidence of benefit. Int J Cancer 2012;131(2):417-425.	Y	N	N	Y	Y	Excluded
13. Moller P, Stormorken A, Jonsrud C, Holmen MM, Hagen AI, Clark N, et al. Survival of pa-	Y	Y	N	Y	N	Excluded Single arm study no control group

Study	P	I	C	O	S	Inclusion / Exclusion
tients with BRCA1-associated breast cancer diagnosed in an MRI-based surveillance program. Breast Cancer Res Treat 2013;139(1):155-161.						
14. Ng AK, Diller LR, Garber JE, Feng Y, Neuberg D, Silver B, et al. A prospective study of breast magnetic resonance imaging (MRI) and mammographic screening in long-term female 62talian lymphoma (HL) survivors. Haematologica 2010;95:S33-S34.	N	Y	Y	N		Excluded (abstract)
15. Obdeijn IM, Winter-Warnars GAO, Mann RM, Hooning MJ, Hunink MGM, Tilanus-Linthorst MMA. Should we screen BRCA1 mutation carriers only with MRI? A multicenter study. Breast Cancer Res Treat 2014;144(3):577-582.	Y	Y	N	N		Excluded Single arm study no control group
16. Passaperuma K, Plewes DB, Causer P, Hill KA, Messner SJ, Wong J, et al. Long-term results of the Toronto magnetic resonance imaging (MRI) breast surveillance study of women with BRCA1 or BRCA2 mutations. J Clin Oncol 2011;1).	Y	Y	N	Y		Excluded Single arm study no control group (abstract of 18.)
17. Passaperuma K, Warner E, Causer PA, Hill KA, Messner S, Wong JW, et al. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer 2012;107(1):24-30.	Y	U	U	U	Y	Excluded
18. Phi XA, Houssami N, Obdeijn IM, Warner E, Sardanelli F, Leach MO, et al. Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age > 50 years: evidence from an individual patient data meta-analysis. J Clin Oncol 2015;33(4):349-356.	Y	Y	Y	N	N	Excluded
19. Saadatmand S, Obdeijn IM, Rutgers EJ, Oosterwijk JC, Tollenaar RA, Woldringh GH, et al. Survival benefit in women with BRCA1 mutation or familial risk in the MRI Screening Study (MRISC). Int J Cancer 2015.	**Y**	**Y**	**Y**	**Y**	**Y**	**Included**
20. Saadatmand S, Vos JR, Hooning MJ, Oosterwijk JC, Koppert LB, de Bock GH, et al. Relevance and efficacy of breast cancer screening in BRCA1 and BRCA2 mutation carriers above 60 years: a national cohort study. Int J Cancer 2014;135(12):2940-2949.	Y	Y	Y	N	Y	Excluded Same trial with mortality outcome included

Study	P	I	C	O	S	Inclusion / Exclusion
21. Santoro F, Podo F, Sardanelli F. MRI screening of women with hereditary predisposition to breast cancer: diagnostic performance and survival analysis. Breast Cancer Res Treat 2014;147(3):685-687.	Y	Y	N	N	N	Excluded
22. 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 63talian 1 study): Final results. Invest Radiol 2011;46(2):94-105.	Y	Y	Y	N	Y	Excluded
23. Speiser D. MRI Screening in brca mutation carriers – the best alternative to prophylactic surgery? Breast Care 2012;7(6):503-504.	Y	Y	Y	Y	N	Excluded (commentary)
24. Tardivon A, Balleyguier C, Cherel P, Paoletti X, This P, Delaloge S, et al. Surveillance of gene mutation carriers with mammography, ultrasound, and magnetic resonance imaging: Results of a multicentric prospective trial (REMAGUS interdisciplinary group). European Journal of Cancer, Supplement 2010;8 (3):224.	Y	Y	Y	N	N	Excluded (abstract)
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):28-36.	Y	Y	Y	N	N	Excluded Review?
26. 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. J Clin Oncol 2011;29(13):1664-1669.	Y	Y	Y	N		Excluded
NEW SEARCH **27. Evans DG, Harkness EF, Howell A, Wilson M, Hurley E, Holmen MM, Tharmaratnam KU, Hagen AI, Lim Y, Maxwell AJ, Moller P. Intensive breast screening in BRCA2 mutation carriers is associated with reduced cancer specific and all cause mortality Hereditary Cancer in Clinical Practice 2016:14(8)**	**Y**	**Y**	**Y**	**Y**	**Y**	**Included**

Appendix 3. Study summary and risk of bias of the included studies

In the following, study summaries and risk of the five included studies are given individually.

Chereau 2010

Characteristics, treatment, and outcome of breast cancers diagnosed in BRCA1 and BRCA2 gene mutation carriers in intensive screening programs including magnetic resonance imaging. Clin Breast Cancer 2010;10(2):113-118

Study type	Prospective study from breast cancer diagnosis
Population	All new breast cancer diagnosed between 2001 and 2007 From Institute Gustav Roussy
Intervention	Annual digital mammography, biannual UL and physical examination, annual MRI
Control	Annual digital mammography, biannual ultrasound and physical examination

Outcome: Mortality	
Breast cancer patients with BRCA 123	
MRI+ 21 (Past history of breast cancer: 14)	Mammography 102 (Past history of breast cancer: 18)
BRCA 1: 15 BRCA 2: 6	BRCA 1: 64 BRCA 2: 38
Follow up: 2.7 years	Follow up: 4.2 years
Breast cancer deaths: 0	**Breast cancer deaths: 16**

Risk of Bias, Chereau 2010

Domain	Review authors' judgement	Risk of Bias Judgement
Bias due to confounding	No adjustment for confounders	Critical
Bias in selection of participants into the study	Participants selected based on previous screening regimen	Moderate
Bias in measurement of interventions	Well defined intervention and probably no effect on outcome	Low
Bias due to departures from the intended interventions	No information	No information
Bias due to missing data	Lacking information but no reason to believe missing data	Moderate
Bias in measurement of outcomes	Probably no effect as mortality is the outcome	Moderate
Bias in selection of the reported result	No a priori plan is present	Moderate
OVERALL BIAS		**Critical**

Evans 2014

MRI breast screening in high-risk women: cancer detection and survival analysis.[Erratum appears in Breast Cancer Res Treat. 2014 Oct;147(3):689

Study type	Prospective studies from enrollment in breast cancer screening programs
Population	Asymptomatic women with a very high breast cancer risk (based on the presence of a proven or likely BRCA1, BRCA 2, or TP53 mutation.)
Intervention	Subset 1: annual MRI (MARIBS) Subset 2: annual MRI and mammography (6 months apart) (NICE)
Control	Mammography: Mammography (does not say how often) No screening: This group has not undergone intensive surveillance, but a subset had undergone a 3 yearly mammography screening program. It is not defined what "not undergone intensive surveillance" is, but we assume this means only screening after age 50 (from Manchester genetic database).

Outcome: Mortality		
MRI+ 959 (647 from MARIBS, 312 from NICE)	Mammography 1223	No screening 557
Breast cancer: 63 (6.5%) (37 MARIBES, 26 NICE) BRCA1: 24 BRCA2: 21 Other: 18	Breast cancer: 76 (6.2%) BRCA1: 27 BRCA2: 30 Other: 19	Breast cancer: 557 BRCA1: 287 BRCA2: 270 Other: 0 (Mutation revealed 4.27 years AFTER breast cancer diagnosis)
Follow up: 11.75 years	Follow up: 6.6 years	
Breast cancer deaths: 3 (4.8%) **BRCA1: 2** **BRCA2: 0** **Family history: 1**	**Breast cancer deaths: 6 (7.9%)** **BRCA1: 2** **BRCA2: 2** **BRCA negative: 2**	**Breast cancer deaths: 109 (19.5%)**
Other cancer deaths: 2 Acute myeloid leukemia: 1 Pulmonary embolus: 1	Other cancer deaths: 3 Ovarian cancer (BRCA1):2 Lung cancer (BRCA2): 1	Other cancer deaths: 12 Ovarian cancer: 12 Other deaths: 7

Risk of Bias, Evans 2014

Domain	Review authors' judgement	Risk of Bias judgement
Bias due to confounding	Analyses were unadjusted	Critical
Bias in selection of participants into the study	Controls selected a posteriori	Moderate
Bias in measurement of interventions		Low
Bias due to departures from the intended interventions		No information
Bias due to missing data		Low
Bias in measurement of outcomes	Outcome assessors were aware of intervention	Low
Bias in selection of the reported result	No a priori plan is presented	Moderate
OVERALL BIAS		**Critical**

Saadatmand 2015

Survival benefit in women with BRCA1 mutation or familial risk in the MRI Screening Study (MRISC). Int J Cancer 2015.

Study type	Prospective cohort from breast cancer diagnosis, with matched controls
Population	Women with breast cancer with a genetic or predisposition for breast cancer (MRISC) 2 308 women (706 BRCA1/2, 2 PTEN, 3 P53, 1597 familial risk)
Intervention	Mammography and MRI
Control	Matched controls not aware of their mutation status, with biannual mammography if 50 years or older

Outcome: Mortality after breast cancer diagnosis	
Breast cancer patient detect by screening program (BRCA or familiar risk)	
MRI+ 93 BRCA 1: 33 BRCA 2: 18 Familiar risk: 41 PTEN: 1	No screening 93 BRCA 1: 33 BRCA 2: 18 Familiar risk: 41 PTEN: 1
During 9 year follow up:	
Local recurrence: 7 Breast specific distant metastasis: 8 BRCA1 mutation metastasis: 3 BRCA2 mutation metastasis: 2 Familial risk group metastasis: 2 PTEN: 1	Local recurrence: 9 Breast specific distant metastasis: 21 BRCA1 mutation metastasis: 9 BRCA2 mutation metastasis: 3 Familial risk group metastasis: 9
MFS after 10 years: 90% BRCA1: 88% BRCA2: 88% Familial: 95%	MFS after 10 years: 77% BRCA1: 72% BRCA2: 83% Familial: 78%
Breast cancer death: 11* **With breast cancer metastasis: 7** **BRCA1: 3** **BRCA2: 2** **Familial: 2**	**Breast cancer death: 20*** **With breast cancer metastasis: 19** **BRCA1: 9** **BRCA2: 3** **Familial: 7**

** p=0.064*

MFS, Metastasis free survival; PTEN, Phosphatase and tensin homolog

Risk of Bias, Saadatmand 2015

Domain	Review authors' judgement	Risk of Bias judgement
Bias due to confounding	Adjusted for lead time bias	Critical
Bias in selection of participants into the study	Controls were selected at breast cancer diagnosis (not intervention group)	Serious
Bias in measurement of interventions	Ascertainment of screening of controls was posterior	Moderate
Bias due to departures from the intended interventions		Moderate
Bias due to missing data		Low
Bias in measurement of outcomes	Outcome assessment was different in controls	Low
Bias in selection of the reported result	No a priori plan was described	Moderate
OVERALL BIAS		**Critical**

Evans 2016, *only Oslo data*

Intensive breast screening in BRCA2 mutation carriers is associated with reduced cancer specific and all cause mortality,Hereditary Cancer in Clinical Practice 2016:14(8)

Study type	All women were followed prospectively from breast cancer diagnosis NOTE: Breast cancer numbers from Oslo study but controls from Evans 2014 (Manchester database)
Population	Asymptomatic women with BRCA2 mutation
Intervention	Annual MRI and mammography (Oslo)
Control	Mammography: Mammography (before MRI were available or late detection of BRCA) (the authors does not say how often) Frequency of screening: 3-yearly mammography at 50-69 years (from Manchester genetic database)

Outcome: Mortality	
MRI+ Oslo: 14	Mammography Oslo: 23
Breast cancer incidence BRCA 2: 14	Breast cancer incidence BRCA 2: 23
Breast cancer death: 0	**Breast cancer death: 3**

Risk of Bias for Evans 2016: same as Evans 2014 due to same trial.

Phi 2016

Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. British Journal of Cancer 2016;114:631-637.

Study type	Systematic review. Pooling individual patient data (IPD) from (30) in meta-analyses .
Included studies	Comparisons of sensitivity and specificity of mammography and MRI in the detection of breast cancers in women with BRCA1/2 mutations
Statistical analyses	To estimate the sensitivity and the specificity of the screening modalities, repeated screening results were summarized to form binomial counts for each woman. For each woman, the number of true-positive and true-negative screens per modality, and the number of total screening visits with or without breast cancer detected were counted. In this way, binomial counts per modality were calculated and analyzed, taking into account that each woman was her own control. As the dependent variable was assumed to follow a binomial distribution, a generalized linear mixed model with logit link function was applied, and the binomial proportions were modelled as a function of modality and BRCA status and conducted separately for sensitivity and specificity. Studies were entered as random-effect variables and study heterogeneities were assumed to depend on modality. The analyses were conducted separately for each age group. To test the differences between the sensitivities and specificities for the three modalities, Wald tests were applied, where the hypothesis was that the difference between the two proportions under study was 0. The number of mammographic screens that would have been needed (NSN) to detect one breast cancer that was missed by MRI was calculated, and stratified according to BRCA mutation, age group and screening round (first or subsequent round). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). P-values o0.05 were considered statistically significant.
Population	BRCA1/2 mutation carriers
Intervention	Group 1: Mammography Group 2: MRI Group 3: MRI and mammography
Control	NA

Outcome: Sensitivity and specificity			
BRCA 1/2 in 1951 women (all ages)			
	Mammography	MRI	Combined
BRCA 1 sensitivity	35.7 (25.9-46.9)	88.6 (73.4-95.6)	92.5 (80.1-97.4)
BRCA 2 sensitivity	44.6 (31.9-58.0)	80.1 (58.9-91.9)	92.7 (79.3-97.7)
BRCA 1 specificity	93.8 (89.3-96.5)	84.4 (78.7-88.8)	80.4 (72.8-86.2)
BRCA 2 specificity	93.4 (88.4-96.3)	85.3 (79.6-89.6)	80.5 (72.8-86.4)

Risk of Bias, Phi 2016 (performed by Juvet and Tjelle)

Critical question	Evaluation
1. Is the method for finding the primary studies described?	YES
2. Is the search itself performed well?	YES
3. Are the inclusion criteria (study design, population, intervention, outcome) well described?	YES
4. Did the review's authors do enough to assess the quality of the included studies?	YES

5. If the results of the review have been combined, was it reasonable to do so?	YES
6. What are the overall results of the review?	Defining specificity and sensitivity of mammography and MRI and in combination
7. How precise are the results?	Confidence intervals acceptable
8. Can the results be applied to the local population?	YES
9. Were all important outcomes considered?	YES
10. Are the benefits worth the harms and costs?	Not relevant
Overall risk of Bias	**Low**

Critical Appraisal Skills Programme (CASP) Systematic Review Checklist 13.03.17, http://www.casp-uk.net/casp-tools-checklists

Appendix 4. Progress log

Progress log

Date	Correspondence
April, 2014	The commissioning forum commissioned a heath technology assessment
January 2015	Dialogue and meeting with expert first time
2015 -2016	Stop in project evaluation due to employees have terminated their employment relationship with FHI.
January 2017	Started project again
October 2017	Dialogue and meeting with expert last time
January 10, 2018	Norwegian Institute of Public Health external review process finish
March 6, 2018	Norwegian Institute of Public Health internal review process finish
	Report Submitted Nye Metoder
	Report available at FHI website

Appendix 5. Study protocol

Clinical effect and cost-effectiveness of screening women with BRCA mutations using MRI and mammography

Prosjektnummer:	1019
Plan utarbeidet (dd.mm.yyyy):	02.02.2015

Kort beskrivelse/sammendrag (norsk)

BRCA1 og BRCA2 genetiske mutasjoner er viktige risikofaktorer i bryst og eggstokkreftetiologi. Disse mutasjonene er sjeldne i befolkningen generelt, men kvinner som bærer en av disse mutasjonene har en høy risiko for å få bryst eller eggstokkreft.
Tidlig deteksjon og risikoreduksjon vil være nyttig og strategier som foreslås er screening ved hjelp av mammografi og / eller magnetisk resonans imaging (MRI), profylaktisk mastektomi og ooforektomi. Mens profylaktisk mastektomi er beskrevet i norske retningslinjer som det beste alternativet for å redusere risikoen for brystkreft, foretrekker de fleste norske kvinner heller en årlig brystkreftscreening ved hjelp av mammografi og MRI. For å være i stand til å forebygge eller behandle brystkreft i denne gruppen av kvinner med høy risiko for brystkreft, er det viktig å finne ut hvilket forebyggende tiltak som er mest effektivt og kostnadseffektivt. I tillegg, vil det hjelpe disse kvinnene å gjøre personlige valg. Vi har blitt bedt om å vurdere klinisk- og kostnadseffektivitet av brystkreftscreening ved MR eller MR og mammografi hos kvinner med BRCA1 / 2-genfeil.

Short description and summary (English)

BRCA1 and BRCA2 genetic mutations are important risk factors in breast and ovarian cancer aetiology. These mutations are not very common in the general population, but women carrying one of these mutations have a high life-time risk of contracting breast or ovarian cancers.
Current strategies proposed for early detection and risk reduction are screening using mammography and/or magnetic resonance imaging (MRI), prophylactic mastectomy and oophorectomy. While Norwegian national clinical guidelines describe prophylactic mastectomy as the best option to reduce breast cancer risk, most women in Norway prefer to have annual breast cancer screening using both mammography and MRI. It is important to ascertain which preventive measure is most effective and cost-effective. This information would help determine appropriate methods for preventing and treating breast cancers among women with high breast cancer risk, and would help these women make personal choices. We have been asked to assess the

clinical- and cost-effectiveness of breast cancer screening using MRI alone or in combination with mammography in women with BRCA1/2 mutations.

Project category and commissioner	
Product (program area):	Health Technology Assessment
Thematic areas:	Secondary Prevention Cancer Health Technology assessment
Commissioner	RHF-Bestillerforum
Project management and participants	
Project manager:	Elisabeth Couto
Responsible for the project:	Marianne Klemp
Internal project participants:	Ingrid Harboe Arna Desser
Plan for replacement by project participants' absence:	Replacements will be decided by the person responsible for the project (MK)
Internal reviewers:	Lene Kristine Juvet Vida Hamidi
External reviewers:	Turid Aas (Haukeland universitetssjukehus) Ellen Schlichting (Oslo universitetssjukehus)

Mandate

Under the new National system for managed introduction of new methods in specialist health services (*Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten*), a health technology assessment (HTA) was ordered to ascertain the clinical and cost-effectiveness of breast cancer screening using magnetic resonance imaging (MRI) alone or in combination with mammography in women with BRCA1/2 genetic mutations.

Goal

Overall objective

- To conduct an HTA to examine breast cancer screening using MRI alone or in combination with mammography and mammography in women with BRCA1 or BRCA2 genetic mutations.

Specific objectives

- To conduct a systematic review to assess the possible effect of breast cancer screening using MRI alone or in combination with mammography on mortality in women with BRCA1 or BRCA2 genetic mutations.
- To conduct a cost-effectiveness analysis of breast cancer screening using MRI alone or in combination with mammography

Background

Up to 10 percent of breast cancers are thought to be due to a genetic predisposition to the disease. BRCA1 and BRCA2 genetic mutations are important risk factors in breast cancer aetiology. These “breast cancer genes” were identified in 1994 (4), and in 1995 (5), respectively. BRCA1 and BRCA2 genes are tumour suppressor genes (6-9).

These mutations are not very common in the general population, with an overall prevalence of *BRCA1/2* mutations reported to be from 1/400 to 1/800 (66-68). Estimates indicate that 3% of Norwegian ovarian cancer patients carry a BRCA1 mutation (69). A systematic review of international studies reported prevalence rates for BRCA1 and BRCA2 mutations in breast cancer cases ranging between 0.7% (95 % CI: 0.3-1.3) and 6.0% (3.8-8.8) for BRCA1 mutations, and between 1.1% (0.4-2.2) and 3.9% (2.2-6.3) for BRCA2 mutations (70).

Women with BRCA1 or BRCA2 genetic mutations have a high lifetime risk of developing breast or ovarian cancers. A published combined analysis of 22 studies reported cumulative breast cancer risks by age 70 of 65% (95% CI: 51-75) and 45% (95% CI: 33-54) for BRCA1 and BRCA2 mutations carriers, respectively (15). For ovarian cancer, the cumulative risk by age 70 was 39% (95% CI:22-51) for BRCA1 mutation carriers, and 11% (95% CI: 4.1-18) for BRCA2 mutation carriers (15). Identifying women who are at high-risk of breast or ovarian cancers could have important public health implications if efficacious strategies were offered to prevent and treat these diseases.

The rate of prophylactic mastectomy varies geographically, with the highest reported rate in the United States (71). In Norway, the rate of prophylactic mastectomy is among the lowest, while rate of prophylactic oophorectomy is among the highest (71). Most women carrying a BRCA mutation have regular mammograms (71). Prophylactic mastectomy has been described as a "decision difficult to make" (72) or a "drastic decision" (73), which might explain that mutation carriers prefer to opt for breast cancer preventive measures such as screening.

To be able to adequately prevent or treat breast cancers in this group of women with high breast cancer risk, it is important to ascertain which preventive measure is the most efficacious. We will therefore assess the clinical- and cost-effectiveness of breast cancer screening using MRI alone or in combination with mammography in women with BRCA1/2 mutations.

Methods

Criteria of selecting studies for this HTA

Type of studies

We will first search for published HTA reports or systematic reviews (SR). If HTA report(s) or SR(s) of high quality answering our objectives (or some of them) are identified, we will use those to write our report. If these HTAs or SRs are based on literature searches that are older than one year, we will increment the HTA or SR with newly published studies. When possible, we will perform updated meta-analyses.

If no HTA reports or SRs of high quality are identified, we will include randomised controlled trials (RCTs) or prospective cohort studies with control group.

Type of participants (Population of interest)

Women aged 18 and above who have or possibly have a BRCA1 or BRCA2 genetic mutation

Types of interventions

Screening for breast cancer using MRI alone or in combination with mammography.

Comparison groups

- No intervention
- Mammography alone

Types of outcome measures

Our main aim is to include only studies examining the following primary outcomes:

Primary outcomes

- Overall mortality
- Overall cancer mortality

- Breast cancer mortality

However, if we identify no studies considering these primary outcomes, we will include studies that investigated the following secondary outcome:

Secondary outcomes:

- Breast cancer incidence

The literature search and publications selection

The literature search

We will systematically search the literature using the following databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- Embase 1980 to present
- Cochrane Library; Cochrane Database of Systematic Reviews, Other Reviews, Technology Assessments, Cochrane Central Register of Controlled Trials (Central)
- Centre for Reviews and Dissemination; DARE, HTA
- ISI web of Science
- PubMed (epub ahead of print)

The literature search will be carried out using selected index terms and free text terms relating to population and intervention. All retrieved articles published in the period covered by these databases until the date of search will be considered. The search will be supplemented with relevant papers found in bibliographies of selected articles. Clinical Trials.gov and WHO ICTRP will be searched to identify relevant ongoing trials. The literature search will be prepared and performed by a research librarian/information specialist in collaboration with the research team.

Publications selection process

Articles will be selected following a two-step strategy: 1) Titles and abstracts of retrieved articles will be independently assessed by two persons to determine relevant full-length articles to be examined, 2) Full-text articles will also be independently assessed by two persons to decide which articles to include in the systematic review. Both steps will be carried out considering inclusion criteria. Disagreement at either stage will be settled by discussion or consultation with a third person.

Ascertaining quality of SR and risk of bias of individual included studies

Assessment of quality of SR(s)

The quality of possible identified SR will be ascertained using the PRISMA checklist for SR (74).

Risk of bias

Individual included studies will be assessed for possible risk of bias using the Cochrane methodology for assessing risk of bias (75). This will be done separately for RCTs and cohort studies.

We will assess risk of bias of RCTs using the Cochrane Collaboration tool for assessing risk of bias (75). For cohort studies, this will be done using the Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) (76).

Data collection and analysis

Data extraction

One of the two review authors will extract the data from individual studies. The second will verify the data. The following data will be extracted: study data (authors names, year of publication, design and setting, clinical trial identification), participants characteristics, description of intervention and comparison, and outcomes (number of participants, number of cases, methods used to ascertain outcome data, estimates of risk, variables adjusted for in the statistical analyses, length of follow-up, and loss to follow-up). We will use ITT analyses.

Statistical analyses and presentation of results

If no SR of high quality is identified, data from individual studies will be quantitatively combined. We will perform meta-analyses separately for each study design and outcome using the Review Manager software (RevMan). Random effect models will be used. Estimates of risk ratios and corresponding 95% confidence intervals will be provided.

When possible, we will performed subgroup analyses according to populations examined, examining separately groups of women who have been tested and not for genetic mutations.

If a SR(s) of high quality is identified, we will present risk estimates extracted from the SR(s). If the SR is older than one year, we will update the risk estimates. This will be performed using the statistical methods described in the above section.

Grading the quality of evidence

Two review authors will assess independently the quality of the evidence for each selected outcome. The quality of the evidence will be evaluated using GRADE (Grading of recommendations Assessment, Development, and Evaluation) (77). GRADE provides specific criteria to consider when rating the quality of evidence. This will be done ascertaining the strength of the study design, possible risk of bias, imprecision and inconsistency of the estimates, and indirectness and magnitude of effect, dose response gradient and potential confounding factors. The overall quality of the evidence will be classified as high, moderate, low, or very low for each outcome. The definition for each category is described in the following table.

Table: Definition of each category for GRADE

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different

Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Economic evaluation

To assess the cost-effectiveness of breast cancer screening with annual MRI and mammography compared to other prevention options, we will develop a Markov model to simulate life-time health effects and costs of the different interventions. The model will be based on efficacy data retrieved through the systematic review and relevant Norwegian epidemiological and cost data. We will estimate costs using official Norwegian unit prices. We will conduct a separate search for quality-of-life weights for the events and health states in the model. We will report results for both health sector and societal perspectives. The PICO for the economic evaluation is

Population:	*Women aged 18 and above with high familial breast cancer risk*
Interventions:	*Annual MRI alone or in combination with mammography*
Control:	*Mammography alone*
Outcomes:	*Cost per QALY gained, Cost per life-year gained, Net health benefit, probability of being cost-effective*
Study design:	*Probabilistic Markov model*
Perspectives:	*Health care provider and societal*

We will make the model probabilistic, that is, all uncertain parameters will be included in the model as probability distributions in order to reflect the degree of uncertainty related to these parameters.

If the systematic review uncovers no effect estimates for the primary outcomes (overall, cancer, breast cancer mortality), we will not perform a cost-effectiveness analysis. Instead, we will estimate the cost of annual screening with MRI alone or in combination with mammography of women age 18 and above with a suspected BRCA1 or BRCA2 genetic mutation in Norway.

Activities and schedule

- Carry out the literature search
- Search for inputs to health economic model (health-related quality of life weights, incidence, morbidity, mortality and costs)
- Select studies to include according to inclusion criteria
- Ascertain possible risk of bias
- Build economic model
- Extract data from selected studies
- Extract data for model and enter as probability distributions
- Conduct statistical meta-analyses
- GRADE the quality of the selected evidence on the outcomes
- Run the model

- Produce the report (write report send report for peer-review, modify report according to peer-reviewers comments/suggestions, publish report after approval)

Schedule for the activities associated with this project

Task	Responsible	Start date	Calendar time in days	End date
Write project plan	EC, AD, MK	19.11.2014	13	15.01.2014
Review of project plan	fagfeller	19.01.2015	15	26.01.2014
Approval of project plan	MK, KO-leder	01.02.2014	8	07.02.2015
Search for literature	IH, EC, AD	01.01.2015	21	02.02.2015
Include/exclude studies,	EC, AD	03.02.2015	42	01.04.2015
Exctract data, analyse and grade	EC, AD	02.04.2015	20	04.05.2015
Build and gather data for economic model	AD	12.02.2015	70	14.04.2015
Run economic model	AD	15.04.2015	21	04.05.2014
Write report and article	EC, AD, MK	05.05.2015	20	01.06.2015
Review of report (internal and external)	EC, AD, MK, fagfeller	02.06.2015	20	27.06.2015
Finalize SR report	EC, AD	29.06.2015	10	13.07.2015
Approval of SR report	KO-leder, MK	14.07.2015	14	04.08.2015
Finalize and submit article (possible)	EC, AD, MK	04.08.2015	27	31.08.2015
Publish report	EC, AD, MK, Info-dep	05.08.2015	15	24.08.2015

End date

August 2015

Publication/dissemination

The HTA report will be published as a Kunnskapssenteret report (in English), and possibly also as a scientific article to reach international readers.

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