Breast Cancer Screening in Women with a Familial or Genetic Predisposition

The role of MRI

Borstkanker screening bij vrouwen met een familiaire of genetische predispositie

De rol van MRI

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CONTENTS

CHAPTER 1

Introduction

INTRODUCTION

Breast cancer is the most common cancer in females. Worldwide more than 1 million new cases are diagnosed each year and nearly 600,000 women die from breast cancer.[1] The incidence varies over the world and is highest in the USA, followed by northern Europe. Between 1997 and 2001, each year, in the USA there were diagnosed on average 135 breast cancers per 100,000 women and 27 breast cancer-related deaths per 100,000 women occurred. In total 13% (1:8) of the women in the USA will be diagnosed with breast cancer in their life.[2] In the Netherlands, the incidence is 124 per 100,000 women each year, which means 11,700 new cases in 2002, accounting for almost one third of all cancers in females in the Netherlands. The cumulative lifetime risk of breast cancer in the Netherlands is currently 11% (1:9) and 4% to 5% of Dutch women die from breast cancer.[3]

Several risk factors for breast cancer are known. The most important risk factors are a female gender, a higher age, a mutation in one of the genes with a high susceptibility for breast cancer and a strong family history of breast cancer.[4] Another important risk factor is mammographic breast density. Breast cancer risk is about 5 times higher in women with a dense structure in >75% of the breast compared with women with little or no dense structure.[5] Several hormonal factors are associated with an increased breast cancer risk, such as a young age at menarche, a high age of menopause, nulliparity, a decreasing number of children, a high age at first birth, no breast feeding, oral contraceptive use and hormone replacement (HRT) use.[6] Also exposure of the mammary gland to high-dose ionizing radiation increases the risk of breast cancer.[4] Nutrition plays an undefined role despite of many studies investigating its elements, such as fatty acids, meat, dairy products, fish, and fruit and vegetables. Alcohol intake slightly increases the risk of breast cancer. Obesity and possible decreasing physical activity are associated with an increased risk for breast cancer. These both risk factors are associated with a change in hormonal factors.[7]

A strong family history of breast and ovarian cancer combined with young ages at diagnosis of affected family members is a very important risk factor for breast cancer. To date, mutations in two genes, BRCA1 and BRCA2, are identified with a high risk for breast and ovarian cancer.[8,9] Recently, also a low-penetrance susceptibility gene for breast cancer became identified: Chek2.[10] Apart from these genes, also germline mutations of the high risk cancer genes TP53, PTEN and STK11/LKB1 are associated with breast cancer.[11,12] The remaining cases of hereditary and familial breast cancer are possibly caused by multiple gene mutations with a low-penetrance for breast cancer, environmental factors or a combination of both.[13-15]

HEREDITARY CANCER: RISKS OF BREAST AND OTHER CANCERS

The BRCA1 gene located on chromosome 17q21[16] was identified in 1994.[8] A year later the BRCA2 gene located on chromosome 13q12-13 was identified.[9] BRCA1 and BRCA2 are both tumor suppressor genes that play a role in DNA repair. The BRCA1 gene plays also a

role in checkpoint control. Mutations in either genes are associated with an autosomal dominant inherited form of breast and/or ovarian cancer.[17,18]

The prevalence of BRCA1/2 mutations is estimated as 0.23% in the general Caucasian population and on average 2-3% in breast cancer patients. This percentage is higher in younger breast cancer patients.[19]

Early family-based studies found that mutations in the BRCA1 and BRCA2 genes are associated with high cumulative lifetime risks of breast cancer: for BRCA1 gene mutation carriers the cumulative breast cancer risk is 20% by age 40, 50% by age 50 and 87% by age 70; for BRCA2 this is 12% by age 40, 28% by age 50 and 84% by age 70.[20,21] But the later (population-based) studies found lower percentages: a cumulative lifetime risk of 45-65% for BRCA1 and 40-45% for BRCA2 at age 70 (Table 1).[14,22,23]

Table 1. Cumulative risk of breast cancer in BRCA1 and BRCA2 gene mutation carriers.

	Ford et al[21]	Struewing et al[104] (BRCA1 and 2)	King et al[14]	Antoniou et al[22]	Chen[23]
	Multiple case families	Population based	Population based	Population based	Multiple case families and population based
	%	%	%	%	%
BRCA1 Age					
40	19	-	21	12	14
50	51	33	39	37	28
60	54	-	58	52	41
70	85	56	69	65	46
BRCA2 Age					
40	12	-	17	8	11
50	28	33	34	18	23
60	48	-	48	32	39
70	84	56	74	45	43

In addition to an early onset of breast cancer, bilateral breast cancer commonly occurred in BRCA1 and BRCA2 mutation carriers.[24-28] Studies investigating the risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers show inconsistent results, some found a higher (especially on the long-term) and others a comparable risk compared to sporadic breast cancer patients.[27-30] The cumulative risk of ovarian cancer was in the early family based studies for BRCA1 mutation carriers 23% by age 50 and 63% by age 70; for BRCA2 mutation carriers 0.4% by age 50 and 27% by age 70.[20,21] Also these risk percentages were some lower in later (population based) studies (Table 2).[14,23,31] If no gene mutation is detected or no gene mutation analysis performed, models exist that can estimate the cumulative lifetime risk and age-specific risk of breast cancer based on the family history and sometimes also on hormonal factors and benign breast disease.[32,33]

In addition to breast and ovarian cancer a BRCA1 or BRCA2 mutation can increase the risk of other cancer sites. BRCA1 mutations are associated with higher risk of pancreatic cancer and cancer of uterine body, cervix cancer and prostate cancer in men younger than 65 years.[34] In BRCA2 mutation carriers, increased risks of prostate cancer, pancreatic cancer, gallbladder and bill duct cancer, stomach cancer and malignant melanoma are reported.[35,36]

HEREDITARY BREAST CANCER: PATHOLOGY AND SURVIVAL

Hereditary breast cancer differs from sporadic cancer in various clinical and pathological features. BRCA1-related tumors are found to have more frequent a highly poor grade (grade 3), because of higher scores for mitosis, a high pleomorphism and less tubule formation.[37-39] These tumors have also a very high frequency of p53 mutations, are more likely to be estrogen receptor (ER), progesterone receptor (PgR) and HER-2neu negative[24,40,41] and are more frequently of the medullary histology type and a basal-like phenotype than sporadic breast cancers.[37,42,43] When only invasive ductal carcinomas are compared with those of sporadic controls, BRCA1-related tumors have more frequently a prominent lymphocytic infiltrate and pushing margins.[38]

Despite the evidence of unfavorable pathologic features in BRCA1-related tumors, results of survival studies in BRCA1 mutation carriers compared with sporadic breast cancer patients are inconsistent. Some studies found no difference in survival between women with BRCA1-related breast cancers and women with sporadic breast cancer with comparable age.[24,27,44,45]

Table 2. Cumulative risk of ovarian cancer in BRCA1 and BRCA2 gene mutation carriers.

	Ford et al[21] Multiple case families	Struewing et al[104] (BRCA1 and 2) Population based	King et al[14] Population based	Antoniou et al[105] Population based	Chen[23] Multiple case families and population based
	%	%	%	%	%
BRCA1 Age					
40	1	-	3	2	5
50	23	7	21	11	10
60	30	-	40	21	22
70	63	16	46	40	30
BRCA2 Age					
40	<1	-	2	<1	2
50	<1	7	2	1	4
60	7	-	6	8	11
70	27	16	12	10	22

Other studies found a worse survival among BRCA1 mutation carriers than in women without BRCA1-related breast cancer.[46,47] Possible explanations for these inconsistent results include small sample sizes, different populations, a real difference in survival of different germline mutations, ascertainment bias caused by selection of long-living BRCA1-related breast cancer patients and different methods of correction for this bias.[48] Another explanation for this controversy about survival might be a more worse survival in patients not receiving adjuvant chemotherapy, but not in patients receiving chemotherapy because of a higher sensitivity to chemotherapy in BRCA1-related tumors and a higher frequency of tumors of the medullary histotype in BRCA1-associated patients.[46,49] One small study found that carriers of a BRCA1 or BRCA2 mutation show more often a complete response to neo-adjuvant chemotherapy than controls with sporadic breast cancer.[50]

Breast cancer due to BRCA2 mutations tends to show a higher malignancy grade than tumors of sporadic controls, although the difference is less strong than that between BRCA1-related and sporadic tumors. This higher malignancy grade appears to be caused by less tubule formation; BRCA2-related tumors have no difference in mitotic count or pleomorphism compared to sporadic breast cancer.[37,38] There are no differences in survival between women with a BRCA2-related tumor and women with a sporadic breast cancer adjusted for age and stage.[26,46,51,52]

Less data exist on the histological characteristics of familial non-BRCA1/2 tumors. It is suggested that lobular carcinoma is more common, tumors are of lower malignancy grade, show less pleomorphism and a lower mitotic count than sporadic breast cancers and BRCA1/2-related tumors.[53] Also, ER- and PgR-positive tumors are more common in non-BRCA1/2 patients than in BRCA1 mutation carriers and possibly also more common than in BRCA2 mutation carriers, but ER- and PgR-positive tumors seem less common than in sporadic controls.[54]

The results of survival studies in women with hereditary cancer that is not BRCA1 or BRCA2 attributable are inconsistent. Some of them found a better survival compared with women with sporadic breast cancer, some studies found no differences and others found a worse survival.[55-59]

RISK-REDUCING STRATEGIES

Current risk-reducing strategies in BRCA1/2 mutation carriers include prophylactic mastectomy, salpingo-oophorectomy, or both, and chemoprevention. These strategies are described in chapter 2. For mutation carriers for whom preventive mastectomy is not acceptable, screening is another option aiming at reducing breast cancer mortality by early diagnosis, possibly combined with prophylactic salpingo-oophorectomy and/or chemoprevention. But currently chemoprevention is rarely used as standard risk-reducing method in the Netherlands. In women with a high cumulative lifetime risk of breast cancer due to a family history, but without a proven BRCA1 or BRCA2 mutation, prophylactic mastectomy and prophylactic salpingo-oophorectomy are less frequently offered and screening of the breasts is therefore the main option for reducing breast cancer mortality in this group of high-risk women.

BREAST CANCER SCREENING

In 1964 the first randomized breast cancer screening trial started in New York, the so-called HIP trial.[60] In that study, about one-third of the breast cancers were detected by mammography. This low sensitivity was probably related to the technical quality of mammography in the sixties. In the seventies technology improved,[61] causing the start of several randomized screening trials in Sweden, the UK and Canada. Because of the breast cancer mortality reduction found in most of these randomized trials,[62,63] in many countries nationwide mammographic screening programs were started in the 1980s for women from ≥50 years of age.[64]

In the last decades the awareness of the familial clustering of breast cancer increased. Clinicians realized that in families with an autosomal dominant pattern of transmission of hereditary breast cancer, screening of breasts was indicated in women at risk because of their family history. Screening often started at a young age, 25-35 years. The initial Dutch guidelines consisted of a 6-monthly clinical breast examination, annual mammography and instructions for monthly breast self-examination. The sensitivity of mammographic screening for breast cancer in these young women with dense breast tissue was low, especially in BRCA1/2 mutation carriers.[65,66] In a diagnostic setting, MRI seemed to be a sensitive imaging method, also in young women with dense breast tissue. Therefore in the late 1990s breast cancer screening studies including MRI were being set up in high-risk women. In the Netherlands, the national MRI screening (MRISC) study started in 1999. The main results of this study are described in chapter 3 to 8 of this thesis. An overview of other screening trials, including MRI screening, in high-risk women, is given in chapter 2 of this thesis.

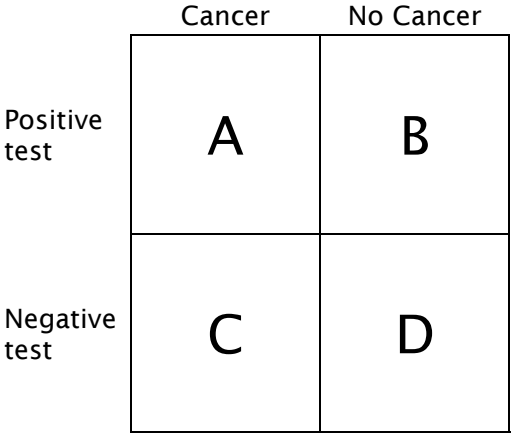
THE EVALUATION OF THE PERFORMANCE OF SCREENING TESTS

Sensitivity and specificity are frequently used test-parameters in the evaluation of screening tests. The sensitivity is the probability that subjects with breast cancer are correctly classified as having breast cancer (also called the true-positive rate). The specificity is the probability of women not having breast cancer correctly classified as not having breast cancer (this is one minus the false-positive rate). Other frequently used test-parameters are the positive predictive value (PPV), this is the percentage of the positive tests that are true-positive and the negative predictive value (NPV), this is the percentage of negative tests that are true-negative (see Figure 1). The PPV and NPV are not only dependent of sensitivity and specificity of a test, but also on the prevalence of the disease in a population. While most tests have a range of results, the test characteristics described are all dependent on the cut-off level for the definition of a positive test.

RECEIVER OPERATING CHARACTERISTIC CURVE

The receiver operating characteristic (ROC) curve is a graphical display of the false-positive rate (one minus specificity) and the true-positive rate (sensitivity) from multiple classification rules. It is used to analyze diagnostic tests and is also used in a screening setting. There are different techniques to compare ROC curves of different tests. Comparison of the entire area under the curve (AUC) of the ROC is the most established technique. The AUC is interpreted as the probability of correctly ranking a randomly chosen subject with the disease and a randomly chosen subject without the disease.[67] Another technique is to focus the comparison on a limited proportion of the curve, the AUC of two ROC curves should compare at similar range of false positive rates or true positive rates. An advantage of this technique is that one can focus on only that part of the ROC curve with clinical relevance. Also, it is possible to choose interesting operating points. It is difficult to compare the accuracy of tests if the sensitivity of one test is higher, but the specificity lower, or vice versa. In the ROC curve it is

possible to compare the true positive rate for every test for a given false positive rate.[68-70] For the determination of an optimal operating point (cut-off level for positive and negative test results) it is important to realize that fewer false-negative test results can only be obtained at the expense of more false-positive results. The location of the interesting operating point depends on the expected utilities and costs associated with true-positive and false-positive test results, the prevalence of the disease and the shape of the ROC curve.[70,71]



Sensitivity (true positive rate)=(A/A+C)*100%.
Specificity=(D/B+D)*100%.
False positive rate=(B/B+D)*100%.
Positive predictive value= (A/A+B)*100%.
Negative predictive value=(D/D+C)*100%.

Figure 1. Measures used in evaluation of screening tests.

FACTORS AFFECTING SENSITIVITY AND SPECIFICITY

The sensitivity and specificity of a screening test do not only depend on the definition of a "positive" and a "negative" test, but also on the characteristics of the different populations studied. Several studies have investigated factors affecting sensitivity and specificity of mammographic screening. In women with a high breast density it is more difficult to detect a tumor, leading to a decreased sensitivity.[72,73] Further, a lower age, also after adjustment for breast density, decreased sensitivity.[74,75] This decreasing of sensitivity is most likely caused by a higher tumor growth rate.[76] Mammography is not only less sensitive in younger women, but also less specific.[77] The lower specificity might also be caused by the higher breast density,[78] because it can mimic breast cancer on mammography. A pre-menopausal status and the usage of HRT are also associated with a lower sensitivity, but it remains unclear if this effect is independent from age and breast density.[72,74,79] In BRCA1/2 mutation carriers a lower sensitivity is repeatedly reported.[65,66] An important reason might be pushing margins in BRCA1/2 mutation carriers, mimicking a benign breast lesion, probably especially in BRCA1 mutation carriers.[80,81] Other reasons might be a higher breast density and tumor growth rate in BRCA1/2 mutation carriers.[53,82,83]

Less is known about factors affecting sensitivity and specificity of MRI. From diagnostic studies we know that hormonal factors influence enhancement behavior of breast tissue. In pre-menopausal women contrast enhancement of breast tissue is lowest in the second week of the menstrual cycle. A pre-menopausal status and the usage of HRT increased contrast enhancement of breast tissue and might decrease sensitivity.[84-86] Although contrast enhancement of MRI is higher in women with dense breasts, only scarcely differences are found between women with dense breasts and almost fatty breasts.[87-89]

PREVALENT AND INCIDENT SCREENING ROUNDS

Screening parameters and tumor characteristics can differ in different screening rounds, especially between first and subsequent rounds. In the first round length-time bias is possibly largest, because in this round more slowly growing tumors, with a longer detectable pre-clinical phase, are detected than in subsequent rounds.[90] This might result in a higher detection rate and sensitivity in the first round.[91,92] Theoretically more large slowly growing tumors should also be found in the first round, but in many screening studies, tumors detected in the first screening rounds are not larger than tumors detected in subsequent rounds.[93] Also specificity can differ between first and subsequent rounds. This parameter is often decreased in the first screening round compared with subsequent rounds because no previous imaging for comparison is available in the first round.[94]

TUMOR GROWTH RATE

Tumor growth rate might influence the calculated sensitivity of a screening test: the higher the tumor growth rate the more interval cancers will appear. Usually, an exponential model for tumor growth is assumed for breast cancer, and the tumor growth rate is often expressed as doubling time. Several studies show that doubling time of breast cancer decreases by age,[95,96] which might partly explain the lower sensitivity in younger women. However it is unknown whether tumor growth is faster at a younger age or, alternatively, fast growing tumors appear earlier in life.[97] In BRCA1/2 mutation carriers a higher mitotic count is found compared to age-matched sporadic breast cancer patients,[53,82] leading to the expectation of a higher tumor growth rate in this group.

BIAS IN THE EVALUATION OF SCREENING PROGRAMS

The most common types of bias occurring in the evaluation of screening studies are selection, lead-time and length-time bias.

- Selection bias occurs because healthier women more often volunteer for screening than less healthy women, causing a lower mortality from breast cancer and other causes in these healthier women than in less healthy women. This bias can only be prevented at the analysis of randomized controlled trial, in which the invited group, including women who do not attend, is compared with a non-invited control group.

- Lead-time bias is demonstrated in Figure 2. Lead-time bias may occur if women diagnosed with breast cancer by screening have a longer survival after diagnosis in comparison with non-screened symptomatic patients, but this does not automatically mean that they live longer. Lead-time leads to biased estimates if survival time after diagnosis of screened breast cancer patients and non-screened breast cancer patients are directly compared.
- Length-time bias occurs because in a screening program more slowly growing cancers possibly with a good prognosis are preferentially detected, because the period between possible detection and the occurrence of symptoms is longer (Figure 3). Because of possible length-time bias it is better to evaluate screening programs by population-based randomized control trials rather than a simple comparison of tumors detected by screening versus tumors presenting clinically.[98,99] Over-diagnosis is an extreme form of length-time bias and may be defined as the detection of cases that would never have come to clinical attention without screening. Estimates of over-diagnosis in breast cancer screening in women 50-75 years varied, but recent studies estimate an over-diagnosis of 10% and 3%.[100,101]

AIMS AND OUTLINE OF THIS THESIS

This thesis describes the main results of the MRISC project. The MRISC project is a breast cancer screening project for women with a familial or genetic predisposition for breast cancer. At the end of the nineties a significant number of women with a hereditary risk of breast cancer asked for preventive strategies. Screening for breast cancer by yearly mammography (possible in combination with oophorectomy) was the main breast cancer mortality risk reducing method for BRCA1 and BRCA2 gene mutation carriers who didn't accept prophylactic mastectomy and for women with a hereditary risk, but no proven gene mutation. Clinicians realize that through the young screening age and as a consequence a frequent high breast density, screening by mammography was less effective than in the population based screening program for women 50-75 years. They were interested in better screening techniques. MRI was a more sensitive imaging method than mammography in a diagnostic setting, especially in young women with dense breasts. A national collaborative group of specialists from different disciplines of 6 familial cancer clinics started in 1999 the MRISC study, in which MRI was added to the screening scheme used at that moment: yearly mammography and 6-monthly clinical breast examination.

This thesis addresses two of the main objectives of the MRISC study:

1. Assessment of the efficacy of screening in diagnosing early-stage breast cancer in women with a familial or genetic predisposition
2. Assessment of the value of MRI in this screening scheme compared to mammography

Further, factors such as different screening rounds, age, risk, menopausal status, breast density, tumor growth rate, tumor characteristics, which might have influence on the efficacy of this screening program and/or the efficacy of the used screening tools are investigated.

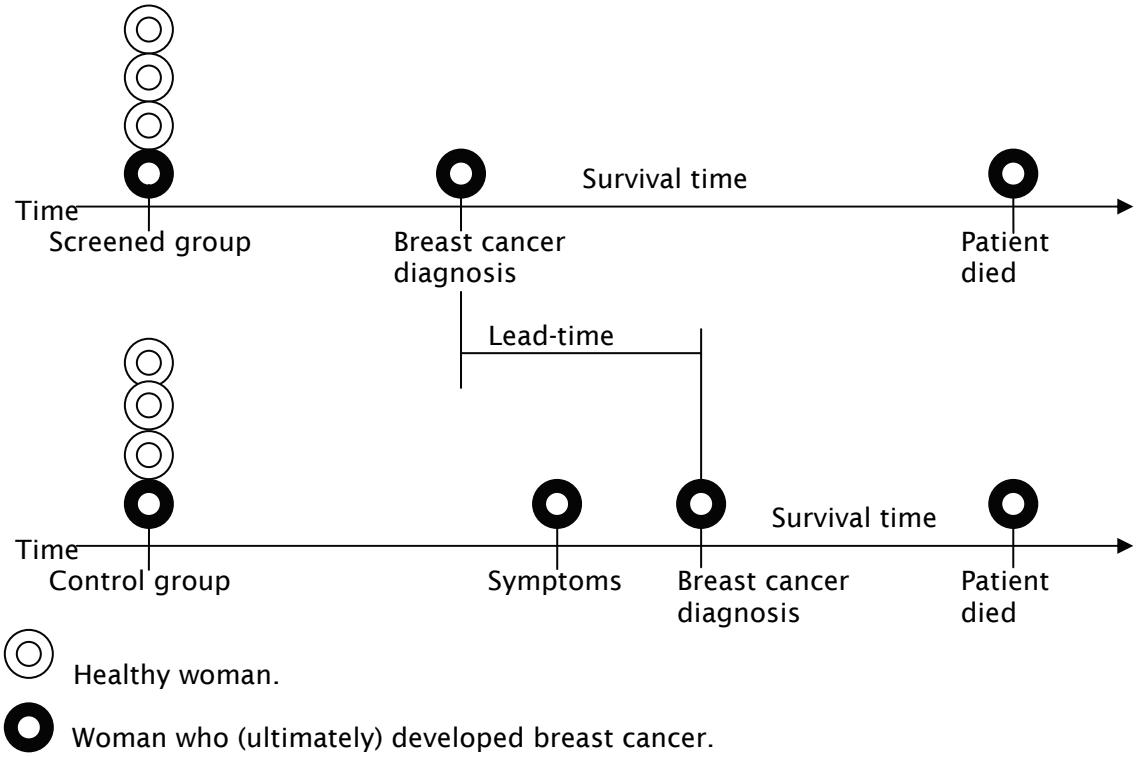


Figure 2. Lead-time bias. In the screened group the breast cancer is diagnosed earlier, resulting in an apparent increase in survival time (lead-time bias), although the time of death might be the same in both the screened and control group.[99]

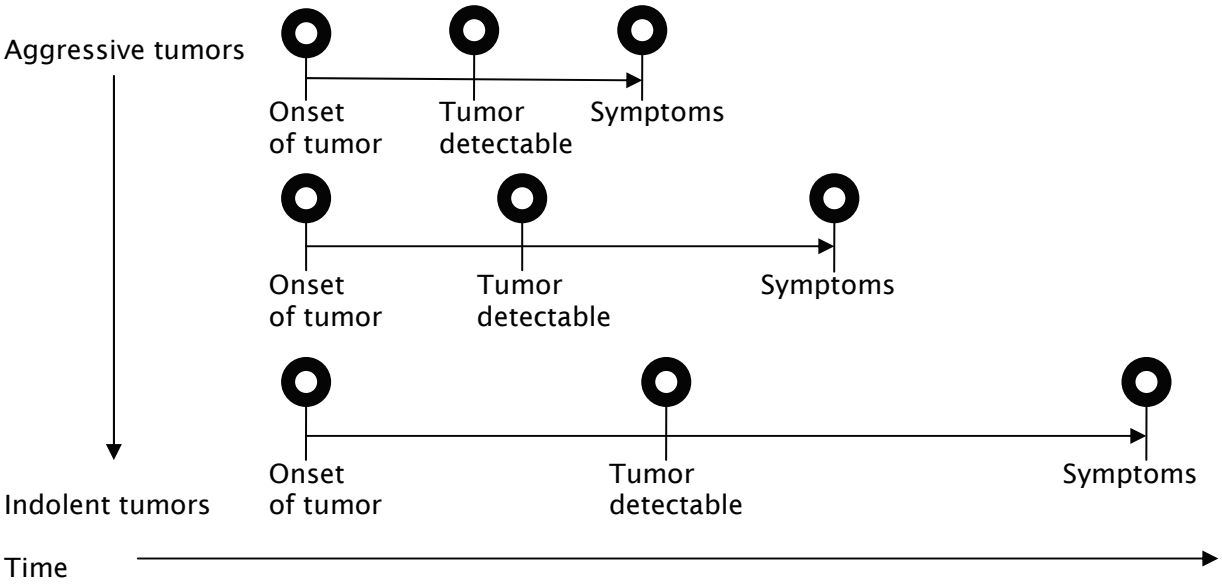


Figure 3. Length-time Bias. Aggressive, rapidly growing tumors have a short potential period that it can detect by screening (period between the tumor is detectable and the occurrence of symptoms). Thus, patients with aggressive tumors are more likely to present with symptoms. More slowly growing tumors have a longer interval between the time that the tumor is detectable and the occurrence of symptoms and are more likely to be detected by screening when they are asymptomatic. As a result, a higher proportion of indolent tumors may be detected in the screened group, causing an apparent improvement in survival.[99]

The other main objectives of the MRISC study are:
3. Assessment of quality of life effects and psychological consequences of screening
4. Assessment of cost-effectiveness of screening

The results of these studies are described in the theses of van Dooren[102] and Rijnsburger.[103]

In chapter 2 of this thesis an overview is given of results of breast cancer screening studies in women with familial and genetic predisposition and the role of MRI in this screening.
The design of the MRISC study is described in chapter 3.
In chapter 4 the efficacy of the MRISC screening scheme is assessed by comparing tumor characteristics of breast cancers detected in the MRISC study group compared with tumor characteristics of two age-matched symptomatic control groups. In addition, the performance of MRI and mammography are compared with respect to various screening parameters (sensitivity, specificity, positive predictive value, area under the curve in the ROC curve).
Differences in screening parameters and tumor characteristics between first and subsequent screening rounds are described in chapter 5. In addition, tumor characteristics detected during the subsequent rounds are compared with those of age-matched controls.
In chapter 6 the role of MRI in the detection of early stage breast tumors is assessed. Tumor characteristics of MRI-detected tumors are described and compared with those of other screen-detected tumors.
In chapter 7 we describe population characteristics that might influence the performance of MRI and mammography. Factors investigated are age, menopausal status, breast density and the presence of a BRCA1 or BRCA2 mutation.
In chapter 8 we compare the tumor growth rate of BRCA1/2 mutation carriers with that of women with a familial predisposition without a proven mutation, accounting for differences in age at diagnosis and menopausal status between these two groups.
In chapter 9 results described in the previous chapters are discussed and compared with results of MRI screening studies in comparable populations. Conclusions are drawn and possibilities for further research described.

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CHAPTER 2

MRI screening for breast cancer in women with a familial or genetic predisposition

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Abstract

Current options for BRCA1/2 mutation carriers to reduce their risk of breast cancer (death) include prophylactic mastectomy, oophorectomy and surveillance. Screening for breast cancer is also offered to women with a familial predisposition for breast cancer, but without a proven BRCA1/2 mutation. The effectivity of mammographic screening in this group of women is questionable, especially in BRCA1/2 mutation carriers, due to a low sensitivity. Magnetic resonance imaging (MRI) appeared to be a sensitive imaging method in the diagnostic setting and is therefore being investigated as screening tool in women at high risk of breast cancer. Results of MRI pilot studies showed a very high sensitivity (100%) of MRI in all studies, while sensitivity of mammography was never higher than 50%. Recently, the first results of four large series were published. In these studies, sensitivity of MRI was lower than in the smaller pilot studies, but all found a higher sensitivity for MRI (71-91%) than for mammography (33-43%). All studies except one found a lower specificity for MRI than for mammography. Characteristics of the tumors detected within the screening program were favorable with respect to size and nodal status. Currently, it appears advisable to offer MRI as a screening tool to proven gene mutation carriers. For genetically susceptible women without a proven gene mutation, more research is warranted to decide which of them should be offered MRI screening.

INTRODUCTION

Breast cancer is the most common cancer in females. Worldwide nearly 1 million new cases are diagnosed each year and 375,000 women die from breast cancer.[1] The incidence varies over the world and is highest in the USA, followed by Europe.

A strong family history of breast and ovarian cancer combined with young ages at diagnosis of affected family members is a high risk factor for breast cancer. To date, two genes are identified with a high-penetrance susceptibility to breast cancer, BRCA1 and BRCA2.[2,3] Recently, a low-penetrance susceptibility gene was also identified: Chek2.[4] Apart from these genes, mutations of the high-penetrance susceptibility cancer genes TP53, PTEN and STK11/LKB1 are associated with breast cancer [reviewed in Refs 5, 6]. The other cases of familial breast cancer are possibly caused by multiple low-penetrance genes, environmental factors or a combination of both.[7,8]

The prevalence of BRCA1/2 mutations is estimated as 0.23% in the general Caucasian population and 2-3% in breast cancer patients. This percentage increases in younger age groups with breast cancer.[9]

Mutations in the BRCA1 and 2 genes are associated with an early onset of breast cancer: for BRCA1 gene mutation carriers the cumulative breast cancer risk is 20% by age 40, 50% by age 50 and 87% by age 70; for BRCA2 it is 12% by age 40, 28% by age 50 and 84% by age 70.[10,11] Population-based studies found slightly lower percentages: a cumulative lifetime risk of 65% for BRCA1 and 45% for BRCA2 at age 70.[12]

If no gene mutation is detected or no gene mutation analysis performed, models exist that can estimate the cumulative lifetime risk and age-specific risk of breast cancer based on the family history, such as the Claus or BRCAPRO model [reviewed in Ref. 13].

RISK-REDUCING STRATEGIES

Current risk-reducing strategies in BRCA1/2 mutation carriers include prophylactic mastectomy, oophorectomy, or both, and chemoprevention. Bilateral prophylactic mastectomy is associated with a more than 90% breast cancer risk reduction (nearly 100%). In the studies of both Meijers-Heijboer et al.[14] and Hartmann et al.[15] no breast cancer cases were detected in the group with preventive mastectomy, while in the study of Rebbeck et al.[16] two breast cancer cases were detected after prophylactic mastectomy in 102 women. One patient had metastatic disease and the other patient developed breast cancer after subcutaneous, not total, mastectomy.[16] Studies about prophylactic oophorectomy report a risk reduction for breast cancer of 53 and 68%.[17,18] Currently chemoprevention is under investigation and not offered as a standard therapy in The Netherlands. A meta-analysis of the tamoxifen prevention trials showed a 38% [95% confidence interval (CI) 28-46] overall reduction in breast cancer incidence.[19] However, in women with estrogen receptor (ER)-negative tumors there was no reduction in the incidence of breast cancer, while the reduction of ER-positive tumors was 48% (95% CI 36-58). As tumors in BRCA1 mutation carriers often are ER-negative it is anticipated that tamoxifen is not an effective chemopreventive agent in these

women, as also suggested by the small study of King et al..[20] However, Narod et al.[21] showed a significant reduction (approximately 50%) of the risk of contralateral breast cancer by tamoxifen treatment in BRCA1 mutation carriers affected with primary breast cancer. Side effects of chemoprevention with tamoxifen include an increase in the incidence of endometrium cancer [relative risk (RR) 2.4 (95%CI 1.5-4.0)] and venous thromboembolic events [RR 1.9 (95% CI 1.4-2.6)].
For mutation carriers for whom preventive mastectomy is not acceptable, screening is another option, aiming reduction of breast cancer mortality, possibly combined with prophylactic oophorectomy and chemoprevention. In women without a proven BRCA1/2 mutation, but with a high cumulative lifetime risk of breast cancer due to a family history these risk-reducing strategies are less frequently offered and screening is therefore the main option for reducing breast cancer mortality.

BREAST CANCER SCREENING

In 1964 the first randomized breast cancer screening trial started in New York,[22] followed by several randomized trials starting in the 1970s.[23] To date, in total eight randomized breast cancer screening trials have been performed in the general population in which about 500,000 women participated. All trials, except the Canadian NBBS1and NBSS-2, showed a breast cancer mortality reduction of 10% or more. The combined results from these trials showed a statistically significant breast cancer mortality reduction of 20-25% in women aged 50-74 years.[23,24] In addition to these randomized trials, several patient control studies were completed. Also these studies uniformly showed a breast cancer mortality reduction in women older than 50.[25] The evidence on the effectivity of screening women aged 40-49 years is more questionable. Although combined results of seven randomized trials, which included women younger than 50 years, showed a significant mortality reduction, this effect may be partly attributed to a mortality reduction because of screening them when they were 50 years or older. Further, the cost effectiveness is not proven.[26,27] Because of the positive results of the randomized trials, in many countries nationwide mammographic screening programs were started. In the United States mammographic screening is recommended for women in their 40s, while in Europe the starting age most times is 50. However, mammographic screening is less sensitive, less specific and less effective for reducing mortality among women aged 40-49 years than in women older than 50 years. Reasons for this observation are the lower incidence of breast cancer, the higher tumor growth rate, the greater tumor heterogeneity and the denser breast tissue in this age category when compared with women aged 50-70.[28-31]
In the Netherlands the breast cancer mortality decreased after the start of the national screening programme[32] and extensive implementation of adjuvant systematic therapy.[33] Although it is difficult to determine which part of the effect is caused by screening and which part by other factors, for example adjuvant treatment, a model simulation predicted that in 2007, adjuvant tamoxifen and chemotherapy would reduce breast cancer mortality with 7% and breast cancer screening with 28-30% in women 55-74 years.[34]

Although clinical breast examination can detect tumors not detected by mammography, it is unproven whether clinical breast examination can detect tumors in a more favorable stage or can reduce breast cancer mortality.[35] Breast self-examination is widely recommended for early detection of breast cancer. The role of breast self-examination is not completely clear, but a meta-analysis suggests that it is an ineffective method to reduce breast cancer mortality.[36]

SCREENING FOR HEREDITARY BREAST CANCER BY MAMMOGRAPHY

Especially after the identification of the BRCA1 and BRCA2 genes in the mid-1990s the demand of screening for breast cancer in women with a high familial risk increased. The efficacy of mammographic screening programs in these high-risk women was investigated in several studies but has never been proven (Table 1).

Table 1. Characteristics of screening programs with yearly mammography (with and without clinical breast examination) in women with a hereditary risk.

Study	No. of women	No. of cancers	Mean follow-up time (months)	Detection rate (‰)	Sensitivity (%)	N+ or Stage 2 (%)
Saetersdal et al.[69]	537	8	First round	15	-	12.5
Moller et al.[70]	1194	29	22	5.8	?	10
Chart and Franssen[71]	1044	24	22	7.3	91	29
Lalloo et al.[72]	1259	14	30	5.5	87	45
Kollias et al.[41]	1371	29	22	9.1	66	35
Lai et al. [73]	2629	34	?	5.7	?	32
Brekelmans et al.[37]	1198	35	35	8.6	74	35
Macmillan[74]	8783	103	12	11.3	?	39
Scheuer et al.[38]	165	12	24	36.2	50	33
Vasen et al.[75]	202	21	?	?	67	20

The detection rate of breast cancer in the screening study of Brekelmans et al.[37] ranged from three invasive cancers in 1000 women years in women with a 15-30% cumulative lifetime risk to 33 invasive cancers per 1000 women years in BRCA1/2 mutation carriers. In women with a 15-30% cumulative lifetime risk this is about three times more than in women of the same age in the general population and for BRCA1/2 carriers even 24 times more frequently. The sensitivity of screening in high-risk women varied from 50 to 91% between different studies and the percentage tumors with positive lymph nodes from 10 to 45% (Table 1). Especially in BRCA1/2 carriers, the sensitivity of mammography was low: Brekelmans et al.[37] found a sensitivity of 56% (5/9) and Scheuer et al.[38] a sensitivity of 50% (6/12) in this subgroup of high-risk women. Possible reasons include a high tumor growth rate, and the atypical mammographic and specific histopathologic characteristics, such as prominent pushing margins, in BRCA1/2 mutation carriers when compared with controls of the same age.[39,40] Only the study of Kollias et al.[41] compared tumor characteristics of a screened high-

risk group with the tumor characteristics of age-matched symptomatic controls and found no major differences with respect to tumor size, nodal status and histological grade.

ALTERNATIVE SCREENING METHODS

Mammography is the only screening method for breast cancer that is extensively evaluated and widely used. In BRCA1/2 mutation carriers and young pre-menopausal women with a high breast density the sensitivity of mammography is relatively low and especially for these groups there is an interest in better imaging methods.

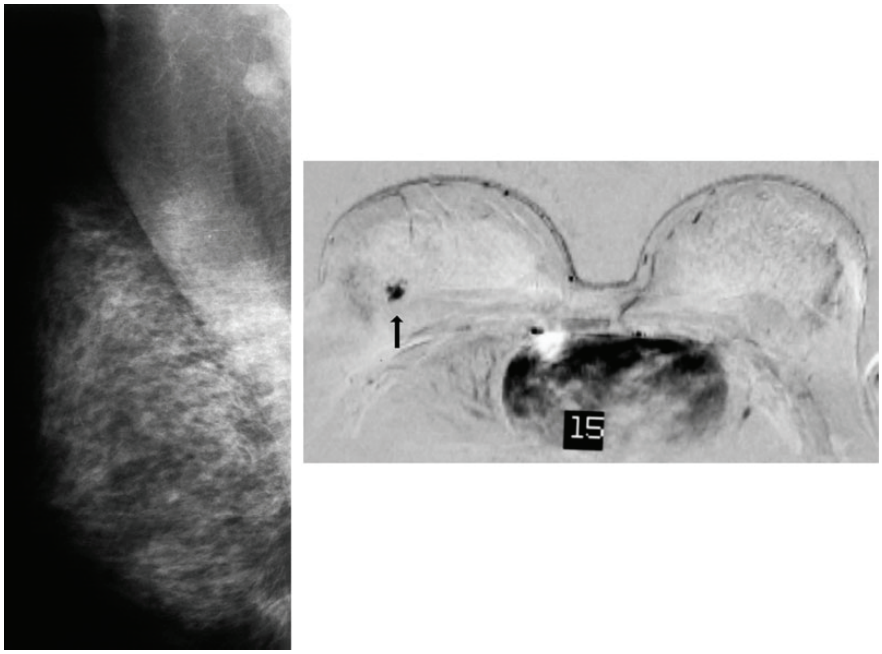

Figure 1. MRI revealing a malignancy in the right breast (see arrow), not visible on mammography of the same patient.

Ultrasound is evaluated in young women with dense breasts and women with a genetic risk for breast cancer. It may be more sensitive, but less specific than mammography.[42-44]
In a diagnostic setting magnetic resonance imaging (MRI) is a sensitive breast imaging modality, especially in detecting multicentric disease (Figure 1). The reported specificity is variable, ranging from 37 to 100%. Benign fibroadenomas and fibrocystic disease cause often false positive MRI results [reviewed in Refs 45, 46]. The reported sensitivity of MRI for ductal carcinoma in situ (DCIS) in a diagnostic setting is variable and ranges from 40 to 100% [reviewed in Refs 47, 48]; especially low grade DCIS is more frequently associated with a slow uptake of contrast and no wash out, mimicking a benign lesion, or showed no contrast uptake.[47-49] While there are few data about the potential of MRI to detect invasive lobular carcinoma (ILC) in a diagnostic setting, the sensitivity of MRI might be slightly lower in comparison with that of invasive ductal carcinoma (IDC). Nevertheless, most lesions are visible on MRI.[50-52] However, also ILC and medullary carcinoma can demonstrate slow uptake of contrast and no wash out or no contrast uptake at all, producing a false-negative examination.[49] On the other hand, in a recent study it was found that MRI was more sensitive

than mammography for IDC, ILC and DCIS.[53] In another study, tumors missed by MRI were characterized by a diffuse growth pattern and small size (<5 mm).[54] These difficulties make it uncertain whether results in the diagnostic setting can be translated to screening programs for high-risk women.

Table 2. Study characteristics of MRI screening studies.

	No. of women	No. of scans	Median follow-up (years)	Mutation carriers n (%)	Previous breast cancer included	Mean or median age (years)	Design
Tilanus-Linthorst et al. * [76]	109	193	2.5 (total)	12(11)	No	41.5 (22-68)	Retrospective
Stoutjesdijk et al. [77]	179	258	?	±32 (18)	No	(21-71)	Retro- and prospective
Podo et al.[78]	105	119	1.75 (total)	?	Yes	46 (25-77)	Retrospective
Morris et al. *[79]	364	364	-	19 (5)	Yes	50 (23-82)	Prospective
Hartman et al. [80]	41	41	1.5 (total)	24 (59)	Yes	42.5 (27-72)	Prospective
Kriege et al.[55]	1909	4169	2.9	358 (19)	No	40 (19-72)	Prospective
Warner et al.[42]	236	457	3 (total)	236 (100)	Yes	47 (26-65)	Prospective
Lehman et al.[81]	367	367	First round	?	Yes	45 (26-86)	Prospective
Leach et al.[56]	649	1881	2.2	120 (18)	No	40 (31-55)	Prospective
Kuhl et al.[44]	529	1452	5.3	43 (8)	Yes	42 (27-59)	Prospective

*MRI Performed only in case of a negative mammography.

MRI SCREENING

In the late 1990s breast cancer screening studies including MRI were being set up in women with a genetic susceptibility. Initially results of small pilot studies were published, recently followed by the first results of four large prospective trials (Tables 2-4). These four large studies had a cross-sectional design, meaning each woman is screened by both mammography and MRI.

All small pilot studies described a very high sensitivity (100%) of MRI, but specificity of MRI appeared lower than that of mammography. This extremely high sensitivity was not confirmed in the larger series published later on (Table 3).

The multicenter Dutch MRISC study had 1909 participants, Including 358 mutation carriers, with a median Follow-up time of 2.9 years.[55] A total of 51 tumors were diagnosed, of which 50 breast cancers. The overall sensitivity was 40% for mammography and 71% for MRI. For invasive cancers this was 33 and 80%, respectively. Mammography detected five, MRI one of six cases of DCIS. The overall specificity was 95% for mammography and 90% for MRI. To date, this is the only MRI screening study that compared tumor characteristics of screen detected breast cancers with those of age-matched symptomatic controls. Characteristics of

Table 3. Screening parameters of different MRI screening studies.

	Tumors detected (N)	Detection rate/ 1000 scans	Sensitivity		Specificity		PPV		Biopt rate		Positive biopt rate (%)
			MRI (%)	XM (%)	MRI (%)	XM (%)	MRI (%)	XM (%)	MRI (%)	XM (%)	
Tilanus-Linthorst[76]	3 (1xDCIS)	16 (3/193)	100 (3/3)	-	97 (184/190)	-	33 (3/9)	-	2.6 (5/193)		60 (3/5)
Stoutjesdijk[77]	12 (3xDCIS)	47 (12/258)*	100 (12/12)	42 (5/12)	93 (228/245)	96 (240/250)	41 (12/29)	33 (5/15)	?	?	?
Podo [78]	8 (3xDCIS)	7 (8/119)	100 (8/8)	13 (1/8)	99 (110/111)	100 (111/111)	?	?	8 (9/119)	1 (1/119)	89 (8/9)
Morris[79]	14 (8xDCIS)	4 (14/367)	100 (14/14)	-	86 (303/353)	-	-	-	16 (59/367)	-	24 (14/59)
Hartman[80]	1 (DCIS)	24 (1/41)	-	-	-	-	-	-	-	-	-
Kriege[55]	50 (6x DCIS)	12 (50/4169)	71 (32/45)	40 (18/45)	90 (3704/4124)	95 (4017/4124)	7.1 (32452)	8.0 (18/225)	1.3 (56/4169)	0.6 (25/4169)	60 (51/85)
Warner[42]	22 (6x DCIS)	48 (22/457)	77 (17/22)	36 (8/22)	95 (415/435)	99.7 (434/435)	?	?	4.6 (20/435)	0.2 (1/435)	39 (22/56)
Lehman[81]	4 (1xDCIS)	11 (4/367)	100 (4/4)	25 (1/4)	93 (336/363)	98 (356/363)	12.9 (4/31)	12.5 (1/8)	6.5 (24/367)	1.1 4/367	15 (4/27)
Leach[56]	35 (6xDCIS)	19 (35/1881)	77 (27/35)	40 (14/35)	81 (1502/1846)	93 (1725/1846)	7.3 (27/371)	10.4 (14/135)	?	?	56 (9/16)¶
Kuhl[44]	43 (9xDCIS)#	28 (41/1452)	91 (39/43)	33 (14/43)	97 (1370/1409)	97 (1364/1409)	24 (14/59)	50 (39/78)	5.4 (78/1452)	4.1 (59/1452)	?

XM denotes mammography.

*MRI performed on identification, detection rate higher than expected.

¶Only diagnostic surgical biopsies, no core biopsies.

43 tumors in 41 women.

the tumors detected within the screening program group were more favorable when compared with both control groups with respect to tumor size, nodal status and grade of tumor differentiation. In the study group 43% of the tumors were 1 cm or smaller, in the control groups this percentage was only 14 and 13%, respectively. The node positivity rate was 21% in the screened group compared with 52 and 56% in the control groups.

Table 4. Tumor characteristics of breast cancers found within different MRI screening studies. Absolute numbers in brackets.

	% ≤ 1cm	% ≤ 2 cm	% N0
Tilanus-Linthorst[76]	67 (2/3)	100 (3/3)	100 (3/3)
Stoutjesdijk[77]	?	22 (2/9)	56 (5/9)
Podo[78]	?	80 (4/5)	?
Morris[79]	?	100 (6/6)	67 (4/6)
Hartman[80]	-	-	-
Kriege[55]	43 (19/44)	75 (33/44)	79 (33/42)
Warner[42]	56 (9/16)	100 (16/16)	87 (13/15)
Lehman[81]	?	100 (3/3)	100 (3/3)
Leach[56]	44 (13/29)	79 (23/29)	81 (21/26)
Kuhl[44]	38 (9/24*)	92 (22/24*)	79 (19/24*)

* only cancers detected in women without a personal history of breast cancer.

Another study is a Canadian study from Warner et al..[42] In this study 236 BRCA1/2 mutation carriers were included and 22 breast cancers were found with six cases of DCIS. The sensitivity was 36% for mammography and 77% for MRI. Of six cases of DCIS, three were visible on mammography and four on MRI. The specificity (based on biopsy rate) was 99.8% for mammography and 95.4% for MRI. Also in this study, the follow-up policy after a probably benign finding differed between mammography and MRI. Tumor characteristics of detected cancers were favorable: 56% (9/16) of the invasive cancers was 1 cm or smaller, all invasive cancers were 2 cm or smaller and 87% (13/15) had negative lymph nodes.

In the recently published multicenter British study (MARIBS study) 649 evaluable women were recruited, including 120 (19%) BRCA1/2 gene mutation carriers. During a follow-up period between 2 and 7 years 35 breast cancers (including six cases of DCIS) were detected in a total follow-up time of 1861 years. The sensitivity was 40% for mammography and 77% for MRI, the specificity was 93% for mammography and 81% for MRI. Of the six cases of DCIS, five were visible on mammography and two on MRI. Of the invasive tumors, 38% (11/29) was 1 cm or smaller and 69% (20/29) was 2 cm or smaller, 81% (21/26) had negative lymph nodes.[56]

Kuhl et al.[44] detected 43 breast cancers (including 9 cases of DCIS) in 41 patients in a single-center study in which 529 women participated. Both women with a family and personal history of breast cancer were included. The sensitivity of MRI was 91%, that of mammography 33%. Specificity was 97% for as well MRI as mammography. However, this was a single-center study performed in a highly experienced center. Furthermore, in addition ultrasound was performed every 6 months. Tumor characteristics were presented for the 31 women without a personal history of breast cancer; of these 31 breast cancers, seven were

DCIS (23%), nine of the 24 invasive cancers (38%) were ≤1cm, 22 (92%) were ≤ 2cm and 19 (79%) had negative lymph nodes.

The participants of these MRI screening studies differ with respect to hereditary risk, age and inclusion of women with previous breast cancer (Table 2). Nevertheless, all studies found a higher sensitivity for MRI than for mammography (Table 3). Specificity of MRI varied between 81 and 97%, which might be partly explained by the different definition of this parameter between studies: while some studies defined a test as false-positive only when a biopsy with a negative result was performed, others defined tests as false-positive after a certain BIRADS score of the imaging. Except for the study of Kuhl et al., all studies found a lower specificity for MRI than for mammography. The positive biopsy rate varied between 15 and 89% in the different studies and was 60 and 39%, respectively, in Dutch[55] and Canadian[42] study (Table 3).

There is no randomized study comparing the tumor characteristics of the screened and a non-screened group in women with a genetic risk for breast cancer and it is not expected that this type of study will ever be performed in this setting. Only one study compared the tumor characteristics with age-matched symptomatic external controls,[55] the other studies reported only the tumor stage of the tumors detected in the study (Table 4). The percentage of cases of DCIS in the prospective studies varied from 12 to 38%, which is relatively high, but in agreement with other screening trials. However, detection of DCIS plays only a small role in reducing breast cancer mortality.[57] The percentage of node negative tumors was variable and varied from 56 to 100%. However, the large studies found a favorable tumor stage: in the Dutch, Canadian, British and German study 79, 87, 81 and 79%, respectively, of the tumors were node negative and 43, 56, 38 and 38%, respectively, 1 cm or smaller (Table 4).

As yet, none of the studies investigated mortality reduction because of short follow-up. Predictions of mortality reduction and cost-effectiveness analyses with a computer simulation model (MISCAN) are currently being performed for the Dutch MRISC study.

In addition to breast cancer mortality reduction and financial costs, other important questions include a subgroup analysis for the different hereditary risk and age groups. It is important to offer MRI, an expensive and time-consuming method, only to women for whom MRI has a high additional value. These subgroup analyses are also being performed in the Dutch MRISC study.

PITFALLS AND ADVANTAGES OF BREAST MRI SCREENING VERSUS MAMMOGRAPHY

As mentioned before, breast MRI screening is a costly and time-consuming method, needing very experienced radiologists. Further drawbacks of the MRI include the relative low specificity compared to mammography and the high number of probably benign findings. The possible anxiety and costs caused by these false-positive results have to be taken into account in the decision making about screening. Improvement of the specificity of MRI is very important in order to reduce unneeded additional investigations and additional costs. Neither the technique nor the criteria for interpretation are standardized,[58] and MRI is not feasible in

patients with pacemakers, aneurysm clips or in server claustrophobic patients, and the availability is limited.

An MRI-guided biopsy is sometimes needed to obtain a histologic diagnosis of non-palpable lesions detected by MRI and not visible on mammography or ultrasound, which technique is not available in every center. Different systems exist for MRI-guided biopsy techniques (core and vacuum biopsy), but all have limitations. With many systems only the lateral side of the breast can be accessed and this is often not the shortest way to the lesion. Another limitation is the inability to verify lesion removal in many cases.[59]

Another disadvantage is spontaneous hormone-induced enhancement of the glandular tissue. To decrease this problem, the MRI should preferentially be performed in the second week of the menstrual cycle, otherwise false-positive results may occur.[60]

An intravenous contrast medium is needed and allergic reactions to gadolinium contrast agents may occur, but serious allergic reactions are extremely rare.

A drawback of mammography in comparison with MRI is the radiation risk of mammography. Studies in women treated for Hodgkin disease found that radiation dose is a risk factor for breast cancer.[61] However, the amount of mammography-induced tumors is unknown. Another drawback of mammography is the higher level of reported pain.[62]

QUALITY OF LIFE AND PSYCHOLOGY

The influence of screening on the quality of life and psychological consequences of screening are important issues of investigation. In the general population or in women with a familial or genetic predisposition, important negative effects of screening on the short-term quality of life and general psychological distress were not found.[62-64] However, there were some subgroups of women who appeared to be more vulnerable for psychological distress: younger women (<40 years) excessively examining their own breasts (i.e. at least once a week), women overestimating their own risk of developing breast cancer, and women who were closely involved in the breast cancer process of their sister.[65-67]

Women who were recalled to additional tests experienced increased anxiety, but not more than women without a hereditary risk [reviewed in Ref. 68]. The long-term effects and the effect of a false-positive result have to be studied further.

CONCLUSION

MRI is a much more sensitive method than mammography and can detect invasive tumors that are occult on mammography. However, inconsistent results of sensitivity of MRI in detecting DCIS are reported. Most studies found a lower overall specificity of MRI than of mammography. Screening programs including MRI are able to detect breast cancer in a favorable stage in high-risk women. However, long-term follow-up and ultimately mortality data are needed to more definitively prove that MRI screening can reduce hereditary breast cancer mortality. Currently, it appears advisable to offer MRI as a screening tool to proven gene mutation carriers. For genetically susceptible women without a proven gene mutation, more research is warranted to decide which of them should be offered MRI screening.

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CHAPTER 3

MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch national study (MRISC)

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Abstract

Mammography screening of women aged 50-70 years for breast cancer has proven to be effective in reducing breast cancer mortality. There is no consensus about the value of breast cancer screening in women aged 40-49 years. Five to ten per cent of all breast cancers are hereditary. One of the options to reduce the risk of breast cancer mortality for women with a familial or genetic predisposition is intensive surveillance. However, the effectiveness of mammography screening for breast cancer in these women, who are mainly younger than 50 years, is unproven. Magnetic Resonance Imaging (MRI) might increase the effectiveness of screening in women with a familial or genetic predisposition. This paper describes the design of the Dutch national study for MRI screening in women with a familial or genetic predisposition. The aims of this study are to investigate: the value of regular surveillance in women with a familial or genetic predisposition for breast cancer, the efficacy of MRI as compared to mammography, cost-effectiveness of regular screening and quality of life during surveillance. Included are women with a lifetime risk of familial breast cancer of 15% or more or BRCA1/2 mutation carriers, who visit one of the Dutch family cancer clinics. The aim is to include 2500 women. The study started on 1 November 1999. On 1 January 2002, more than 1700 women, including 210 proven carriers of a BRCA1 or BRCA2 mutation, were included in the study.

INTRODUCTION

Breast cancer is the most common type of cancer in females worldwide, with a high incidence especially in Europe and North America. The cumulative lifetime risk for Dutch women to develop breast cancer is about 10%, with a ten year mortality of about 40%.[1,2]

Randomized studies have shown that mammography screening in women between 50 and 70 years old can reduce breast cancer mortality by about 25-30%.[3,4] Recently, a systematic review disputed these findings.[5] While the debate continues, many experts agree that the criticism is inconsistent and insufficiently funded. Especially since the publication of the update of the 5 Swedish studies, showing a significant reduction in overall mortality,[6] the general opinion is that there remains a sound scientific basis for breast cancer screening. Combining all population based randomized control trials also showed a significant breast cancer mortality reduction in women aged 40-49.[7,8] However, this effect might be partly attributed to a mortality reduction due to screening these women when they were 50 years or older.[7] Because of the lower breast cancer incidence and higher frequency of negative effects of screening,[9] there is no consensus regarding the cost-effectiveness of mammography screening in this age group. No data from randomized trials are available for women under the age of 40. It might be that screening younger women is more cost-effective when it is limited to women with increased risk, such as women with a positive family history or a proven genetic predisposition.

When there is a strong family history, cancer could be inherited. Five to ten per cent of all breast cancers are hereditary. In the Netherlands approximately 20% of familial breast cancer is caused by BRCA1, 5% is caused by BRCA2 and 75% is non-BRCA1/BRCA2.[10] BRCA1/2 gene mutation carriers have a cumulative lifetime risk of breast cancer of 60 to 85%. Women with a familial history or a genetic predisposition for breast cancer often develop the disease at a very young age.[11,12]

One of the options to prevent death from breast cancer for women with increased risk is intensive surveillance. The recent Dutch guidelines for surveillance of women with a familial or genetic predisposition consist of a 6-monthly clinical breast examination, annual mammography and instructions for monthly breast self-examination. The effectiveness of mammography screening for breast cancer in women with a familial or genetic predisposition, who are frequently under the age of 40 years, is currently unproven. A number of studies describe the preliminary results of surveillance by mammography and clinical examination in high risk women.[13-18]

The sensitivity of mammography increases with age.[19] One of the reasons is that pre-menopausal women have denser breasts, making it more difficult to detect tumors than in post-menopausal women.[20,21] Another breast imaging method is Magnetic Resonance Imaging (MRI), which is, in all age groups, a highly sensitive method in a diagnostic setting but the specificity is variable.[22-24] This modality might improve the sensitivity of breast cancer screening in women with high familial risk. There is little experience with MRI as a screening modality compared to mammography.[25-29] Currently, there are large ongoing prospective

national MRI screening studies in several countries, including the United Kingdom[30], Germany[31] and the Netherlands, investigating the effect of MRI screening in women with a familial or genetic predisposition. This paper describes the study design and characteristics of the study group of the national Dutch MRI screening study (MRISC).

OBJECTIVES

The national Dutch study for MRI screening in women with familial or genetic predisposition for breast cancer, called MRISC project (the acronym of MRI Screening or Mamma RISC) is a multidisciplinary project, in which specialists in radiology, epidemiology, oncology, pathology, clinical genetics, psychology and surgery take part. The study is approved by the medical ethical committee of the participating centers and is supported by the Dutch Health Council.

The starting date of the project was 1 November 1999 and the duration will be at least three years. Six family cancer clinics from 2 cancer centers and 4 university hospitals are taking part in the study (Table 1).

The aims of the study are to investigate:

- The value of regular surveillance in women at high risk for breast cancer due to a familial predisposition
- Efficacy of MRI compared to mammography
- Quality of life effects during regular screening
- Cost-effectiveness of regular screening

STUDY POPULATION

In the six participating family cancer clinics, a screening program for breast cancer in women with increased breast cancer risk already existed before the start of the MRISC study. The program consisted of a 6-monthly clinical breast examination, an annual mammography and instructions for monthly breast self-examination. Women who were already under intensive surveillance and women who came for the first time were asked to participate in the study by a clinician.

Inclusion criteria are:

- A life time risk for breast cancer of 15% or more due to a familial or genetic predisposition
- No previous breast cancer
- Aged between 25 and 70 years, or younger than 25 in women from families with very young age of onset (<30 years)
- No evident symptoms of breast cancer

STUDY DESIGN

The methodologically best study design is that of a randomized, controlled trial, with a study group of high risk women who are invited for screening and a control group of high risk

women who were not invited for screening. However, most women with familial or genetic predisposition will not consent to randomization. Because of this ethical aspect, it was not possible to randomize women in a screening and non-screening arm. Therefore the first research question, whether screening is effective compared with no screening, will be investigated by a prospective observational design. This means that the control group of non-screened women must come from an external source (see compared groups).
The second research question, the effectiveness of the mammography compared to MRI, is being investigated in a controlled design, where women annually receive both screening modalities (mammography and MRI). Both imaging modalities will be judged independently by two different radiologists. Later, the results of the two screening modalities will be compared with each other, scoring one modality independently from the other so that every woman is her own control.

Table 1. Summary of the MRISC study.

Starting date of the project	1 November 1999
Participating Centers	-Daniel den Hoed Cancer Center/Erasmus MC, Rotterdam -Netherlands Cancer Institute, Amsterdam -University Medical Center Nijmegen -Leiden University Medical Center -University Hospital Groningen -VU University Medical Center, Amsterdam
Number of women	1500-2500
Duration of the project	at least 3 years
Risk groups	60-85% (mutation carriers)
	30-50%
	15-30%
Age	25-70 years

ENDPOINTS

The aim is to include about 2500 women and to follow them for at least three years. In this population we expect to find 100 invasive and in situ breast cancers.
The primary endpoints of the study are the percentage and incidence of advanced tumors (stage II and higher) in comparison to early stages (DCIS, stage I). The stage of a breast tumor is a good predictor for mortality, also in women under the age of 50.[8]
The intermediate outcome measures of the study include:

- The incidence and stage distribution of tumors at first (prevalent) screening and continued (incident) screening.
- The ratio, stage distribution and time since last screening of interval carcinomas.
- Sensitivity, specificity and positive predictive value of the different screening modalities.
- Quality of life, measuring the physical, psychological and social effects of screening

Empirical data will be incorporated in a model, called the MISCAN model[32] for estimating several screening parameters simultaneously. This detailed and validated model has been especially developed for the evaluation of screening programs. Apart from the early screening parameters, the expected mortality rate, lead-time, tumor incidence caused by radiation and

rate of over diagnosis will be estimated. Further, a cost effectiveness analysis of the screening program will be performed.

COMPARISON GROUPS

For the first research question, screening is compared with non-screening. The percentage of early and advanced tumors in the research population will be compared with a non-screened group of breast cancer patients with comparably increased breast cancer risk.
We plan to use various comparison groups of breast cancer patients:

- The first group is extracted from a population study investigating the frequency of BRCA1 and BRCA2 mutations in a group of unselected symptomatic patients with primary breast tumors. A detailed family history of breast cancer from these patients is available.
- The second group is the non-screened family members with breast cancer of the participating women. This is mainly a historical control group who developed breast cancer before the introduction of screening in women with increased familial risk.
- The third control group is extracted from cancer registration data of all breast cancer patients in the Rotterdam and Amsterdam cancer clinics. Family history of the patients is one of the registered items.

For the second research question, the effectiveness of the different screening modalities is being investigated through the comparison of screening parameters such as tumor detection rate, sensitivity, specificity and positive predictive value.

SURVEILLANCE PROGRAMME

Participants visit the family cancer clinic twice a year. Visit A consists of a clinical breast examination. Visit B consists of a clinical breast examination, a mammography and MRI, if possible on one day. The maximum time period between the performances of the different screening imaging modalities is six weeks. The MRI is preferentially performed between day 5 and 15 of the menstrual cycle, to minimize glandular tissue enhancement.[23] All women receive oral and written instructions for monthly breast self-examination.

RISK STRATIFICATION

One of the inclusion criteria is a cumulative lifetime risk of breast cancer of 15% or more. In this study we distinguish between: group I, BRCA1/2 mutation carriers (>60% cumulative lifetime risk), group II, women with high risk (30-50% cumulative lifetime risk) for breast cancer and group III, women with moderate risk (15-30% cumulative lifetime risk). To determine the cumulative lifetime risk for breast cancer of the women a “decision tree” is made. This tree is an adapted form of the tables of Claus,[33] which predict the cumulative lifetime breast cancer risk of women based on the number of family members with breast cancer, their age at diagnosis and whether they are first- or second-degree relatives. For this study the family history of ovarian cancer is also taken into account.

The lifetime risk categories for breast cancer are indicated in Table 2.

RADIOLOGY AND FOLLOW-UP

Once a year, women receive 2-view mammography and a MRI with gadolinium-containing contrast medium, via a standard protocol. The mammography and MRI are scored in a standard way by the Breast Imaging Reporting and Data System (BI-RADS) classification,[34] blinded from each other. The MRI is preferably performed between day 5 and 15 of the menstrual cycle. When one of the 2 images is scored as BI-RADS "category 3: probably benign finding" or "category 0: need additional imaging evaluation", additional investigation by ultrasound with or without fine needle aspiration is performed or the mammography or MRI is repeated. When one of the two images is scored as BI-RADS "category 4: suspicious abnormality" or "category 5: highly suggestive of malignancy", additional investigation by biopsy is performed. When the imaging is negative, but the clinical breast examination is suspect, additional investigation is also performed.

Table 2. Risk stratification to determine the cumulative lifetime risk for breast cancer.

Group I BRCA1/2 mutation carriers (cumulative lifetime risk 60-85%) 1. Proven or obligate mutation carriers
Group II High risk (cumulative lifetime risk 30-50%). Women with: 1. A first-degree family member with a BRCA1/2 mutation 2. A first-degree-family member and two other first or second degree family members affected with breast or ovarian cancer 3. Two first-degree or one first and one second-degree family members with breast cancer, mean age at diagnosis 45 years or younger.
Group III Moderate risk (cumulative lifetime risk 15-30%). Women with: 1. A second-degree family member with a BRCA1/2 mutation. 2. One first-degree family member with breast cancer younger then 40 years 3. Two first-degree family members or one first- and one second degree family member with breast cancer together, mean age at diagnosis between 45 and 60 years. 4. Three second-degree family members with breast or ovarian cancer 5. Two first or one first and one second-degree family members, 1 affected with breast cancer younger than 55 and one with ovarian cancer

RADIOLOGICAL REVISION

All pairs with a different classification between mammography and MRI (so-called discordant pairs) will be reviewed by expert radiologists from a different participating center. To determine what pairs have a different result (are discordant), 3 different imaging groups have been constructed:

1. Negative/benign (BI-RADS classification 1 or 2
2. Probably benign/additional imaging needed (BIRADS classification 3 or 0)
3. Probably malignant (BI-RADS classification 4 or 5)

When the mammography and MRI are classified in different groups, this is defined as a discordant pair.

PATHOLOGY ASSESSMENT AND REVISION

Histopathologic characteristics of all cytology and histology are registered on standard forms, developed especially for this project. Registered characteristics are, among others, tumor size, morphology of benign and malignant lesions, Bloom and Richardson histologic grade, nodal status, and ER and PgR status. To guarantee a consistent classification, expert pathologists review all benign and malignant material.
To determine the representativeness of the histopathologic material, this is also reviewed together with the imaging by a team of expert pathologists and radiologists. The aim is to determine the correlation between the histopathologic material and the imaging.

DATA COLLECTION

In every participating center, data are collected on family history of breast cancer, mutation status for BRCA1/2, hormonal factors, screening history before the study, information about every screening visit and outcome, including clinical breast examination, mammography, MRI and additional research and pathology. Standard registration forms were especially developed for this project. The data are entered in a database and regularly updated. In women who develop a malignancy, treatment data are registered. These women are followed to register the occurrence of recurrence, second primary tumors and survival.

CHARACTERISTICS OF THE STUDY GROUP

Until January 2002, 1764 women have been included in the study. See Table 3 for the characteristics of the first participants entered in the database. The mean age of the first 1374 women is 41 years (range 19-70 years).

DISCUSSION

There is no consensus regarding the most efficient surveillance method of women with familial or genetic predisposition for breast cancer. Several studies suggest that conventional screening by mammography and physical examination is inadequate, especially in proven carriers.[13,26] Recent studies suggest that MRI might be more sensitive than mammography.[25,27,28] However, these studies described small populations[25,27,28] including retrospective data,[27] included heterogeneous groups of women[25,28] or had a follow-up scheme after a suspicious MRI that differed from that after a suspicious mammography.[25] In this way the sensitivity (and specificity) of MRI might be artificially increased. Further in these studies, tumor stage at detection was highly variable. There is no consensus about specificity of MRI compared to mammography. Large-scale prospective studies, such as the Dutch MRISC study, in well-defined high-risk populations are needed that guarantee the independent assessment of MRI and mammography. These studies might answer the question whether screening can really be effective in reducing breast cancer mortality in women with familial or genetic predisposition and at what cost.

Table 3. Patient characteristics of the first 1374 women analyzed in the MRISC study.

	N	%
Age categories		
< 30 years	169	12
30-39 years	500	37
40-49 years	442	32
50-59 years	226	16
≥ 60 years	37	3
Lifetime risk for breast cancer		
60-85%	210	16
30-50%	718	55
15-30%	370	29
Menopausal status		
Pre-menopausal	1051	67
Peri-menopausal	41	3
Post-menopausal (including hysterectomy)	245	16
Unknown	226	14
Previous screening		
No	176	11
Only clinical breast examination (CBE)	28	2
Imaging (with or without CBE)	1338	87

Total numbers in categories can differ due to missing data.

In conclusion, preliminary results from the ongoing Dutch MRISC study suggest that it is possible to identify young women at high familial and genetic risk for breast cancer. Screening of women with familial or genetic predisposition for breast cancer by MRI appears to be feasible within the context of a national study. In the near future, this and other ongoing large-scale prospective studies hope to define the most adequate surveillance scheme for women with familial or genetic predisposition.

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CHAPTER 4

Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition

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Abstract

Background The value of regular surveillance for breast cancer in women with a genetic or familial predisposition to breast cancer is currently unproven. We compared the efficacy of magnetic resonance imaging (MRI) with that of mammography for screening in this group of high-risk women.

Methods Women who had a cumulative lifetime risk of breast cancer of 15 percent or more were screened every six months with a clinical breast examination and once a year by mammography and MRI, with independent readings. The characteristics of the cancers that were detected were compared with the characteristics of those in two different age-matched control groups.

Results We screened 1909 eligible women, including 358 carriers of germ-line mutations. Within a median follow-up period of 2.9 years, 51 tumors (44 invasive cancers, 6 ductal carcinomas in situ, and 1 lymphoma) and 1 lobular carcinoma in situ were detected. The sensitivity of clinical breast examination, mammography, and MRI for detecting invasive breast cancer was 17.9 percent, 33.3 percent, and 79.5 percent, respectively, and the specificity was 98.1 percent, 95.0 percent, and 89.8 percent, respectively. The overall discriminating capacity of MRI was significantly better than that of mammography ($P<0.05$). The proportion of invasive tumors that were 10 mm or less in diameter was significantly greater in our surveillance group (43.2 percent) than in either control group (14.0 percent [$P<0.001$] and 12.5 percent [$P=0.04$], respectively). The combined incidence of positive axillary nodes and micrometastases in invasive cancers in our study was 21.4 percent, as compared with 52.4 percent ($P<0.001$) and 56.4 percent ($P=0.001$) in the two control groups.

Conclusions MRI appears to be more sensitive than mammography in detecting tumors in women with an inherited susceptibility to breast cancer.

INTRODUCTION

The cumulative lifetime risk of breast cancer among Dutch women is approximately 11 percent.[1] A family history of breast cancer or the presence of a germline-mutation of the BRCA1 or BRCA2 gene increases this risk considerably and is often associated with a diagnosis at a young age.[2,3] Among high-risk women, the risk of breast cancer can be reduced by prophylactic mastectomy,[4,5] prophylactic oophorectomy,[6,7] or chemoprevention.[8] Early diagnosis as a result of intensive surveillance may also decrease the rate of death from breast cancer.

Randomized trials have shown that mammographic screening of all women who are between 50 and 70 years of age can reduce mortality from breast cancer by about 25 percent.[9] Although these findings were recently disputed,[10] there is a consensus among clinicians that breast-cancer screening of women in this age group is effective. Screening is one of the main factors contributing to the decrease in mortality associated with breast cancer in the Netherlands.[11] However, there is no consensus about the value of breast-cancer screening among women who are 40 to 49 years old.[12-14] One of the reasons for the lack of agreement is the difficulty in detecting tumors by mammographic screening in younger women, who have denser breasts than post-menopausal women.[15,16] Although screening is frequently offered to women with a genetic predisposition to breast cancer who are under the age of 50 years, the efficacy of this approach is unproven. Preliminary results of surveillance by mammography and clinical breast examination in such women showed that mammographic screening has a low sensitivity for detecting tumors, especially in carriers of a BRCA mutation.[17-21] Possible reasons, apart from the high rate of growth of tumors in women with such mutations, include the atypical changes seen on screening mammograms and specific histopathological characteristics in carriers of BRCA mutations, as compared with non-carriers of the same age.[22-24]

In a diagnostic setting, magnetic resonance imaging (MRI) is a sensitive method of breast imaging, and it is virtually uninfluenced by breast density, but the specificity is variable and the costs are high.[25-27] Because MRI may improve the sensitivity of screening in women with a familial or genetic predisposition to breast cancer, we prospectively compared MRI with mammography for screening women with such a predisposition in order to determine whether screening with MRI facilitated the early diagnosis of hereditary breast cancer.

METHODS

Study population

The design of our MRI screening study, in which six subcommittees in different disciplines were involved, has been described previously.[28] Between November 1, 1999, and October 1, 2003, 1952 women with a genetic risk of breast cancer were recruited for the study by six familial-cancer clinics in the Netherlands. The six centers were Erasmus Medical Center-Daniel den Hoed Cancer Center, Rotterdam; the Netherlands Cancer Institute, Amsterdam;

University Medical Center Nijmegen, Nijmegen; Leiden University Medical Center, Leiden; University Hospital Groningen, Groningen; and Free University Medical Center, Amsterdam. The study was approved by the ethics committees of all the centers. All the women who participated gave written informed consent.

The inclusion criteria for participation were a cumulative lifetime risk of breast cancer of 15 percent or more owing to a familial or genetic predisposition, according to the modified tables of Claus et al.,[29] and an age of 25 to 70 years. Women could be tested at an age younger than 25 if they had a family history of breast cancer diagnosed before the age of 30 years, since testing began at an age 5 years younger than that at which the youngest family member was found to have breast cancer. Women with symptoms that were suggestive of breast cancer or women who had a personal history of breast cancer were excluded.

Surveillance

Surveillance consisted of a clinical breast examination performed by an experienced physician every six months and imaging studies performed annually by experienced radiologists. The imaging included a mammographic study (oblique and craniocaudal views and, if necessary, compression views or magnifications) and a dynamic breast MRI with gadolinium-containing contrast medium according to a standard protocol.[25] Whenever possible, both imaging investigations were performed on the same day or in the same time period, between day 5 and day 15 of the menstrual cycle. The results of mammography and MRI were scored in a standardized way, according to the Breast Imaging Reporting and Data System (BI-RADS) classification,[30,31] and the results were blinded so that the two examinations were not linked. When one of the examinations was scored as either BI-RADS category 3 ("probably benign [i.e., uncertain] finding") or category 0 ("need additional imaging evaluation"), further investigation by ultrasonography with or without fine-needle aspiration was advised, or mammography or MRI was repeated. When one of the two examinations was scored as BI-RADS category 4 ("suspicious abnormality") or category 5 ("highly suggestive of malignancy"), a cytologic or histologic evaluation of a biopsy specimen was performed. When the results of mammography and MRI were negative but the findings on clinical breast examination were rated as uncertain or suspicious, additional investigation was also performed. The diagnosis of malignant tumors was based on the results of a histologic examination. One of the investigators, an expert pathologist, reviewed all the biopsy specimens that formed the basis for the diagnosis of breast cancer.

Statistical analysis

The women were divided into three categories according to the cumulative lifetime risk of breast cancer, as follows: carriers of the BRCA1 or BRCA2 or other mutations (cumulative lifetime risk, 50 to 85 percent), a high-risk group (risk, 30 to 49 percent), and a moderate-risk group (risk, 15 to 29 percent).[28,29] The characteristics of the women in each risk group were compared by analysis of variance or Pearson's chi-square test.

The rates of detection of breast cancer for the group as a whole and for each of the three risk groups were calculated, and a Poisson distribution was assumed in order to calculate the 95

percent confidence intervals. Person-years at risk were calculated from the date of the first examination, irrespective of the type of examination, to the date of detection of breast cancer, bilateral prophylactic mastectomy, or death; the date that a patient stopped surveillance; or the cutoff date for this analysis (October 1, 2003). An "interval cancer" was defined as a carcinoma detected between two rounds of screening after initially negative findings on screening. In our analysis, we defined as positive a mammographic or MRI study with a BI-RADS score of 0, 3, 4, or 5 and a clinical breast examination that was classified as "uncertain" or "suspicious," because those were the results that triggered an additional examination.

To compare the three different screening methods, we calculated the sensitivity, specificity, and positive predictive value of each. The sensitivity used is that of one screening method relative to the others, meaning that a test result is a false negative when a proven cancer (diagnosed on the basis of a histologic examination) is detected in the interval or by one of the other methods. Receiver-operating-characteristic (ROC) curves for the two imaging methods were generated. The area under the curve was used as an index in evaluating the inherent capacity of a screening method to discriminate between "positive" and "negative" cases. We used a z-test to compare the area under the curve for the results of mammography and MRI. For the analysis of the screening variables, we used only the screening data that included the results of both mammography and MRI.

To determine whether breast cancer was diagnosed by screening at a stage more favorable to treatment, the characteristics of breast tumors detected in the study group were compared with those in two control groups. The first control group was derived from all women who had breast cancers diagnosed in 1998 in the Netherlands. These data were obtained from the National Cancer Registry. The second control group consisted of unselected patients who had received a diagnosis of primary breast cancer in Leiden or Rotterdam between 1996 and 2002 and who were participating in a prospective study of the prevalence of gene mutations.[32] Subjects in both control groups were matched for age with the patients in the study group (in five-year categories). From this series of consecutive patients in the second control group, we chose all the unscreened patients who were between 25 and 60 years old and whose cumulative lifetime risk of breast cancer was more than 15 percent because of a family history of the disease — information that was routinely recorded in this database. The differences in tumor characteristics between the study group and the control groups were tested with the use of Pearson's chi-square test or the chi-square test for trend. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS software (version 9.0).

RESULTS

Study Population

Of the women who were invited to participate in the study, 90 percent agreed. Initially, 1952 women were included; 8 withdrew from the study before their first screening visit and another 35 were excluded because they ultimately proved not to be carriers in a family with a proven

mutation and there fore had less than a 15 percent cumulative lifetime risk of breast cancer. Of the 1909 remaining women, 88 (4.6 percent) left the study or were lost to surveillance before October 1, 2003; 65 of these 88 women underwent prophylactic mastectomy. Another 89 women (4.7 percent) remained under surveillance but later refused screening by MRI, because of claustrophobia or for other reasons.

Table 1 lists the characteristics of the 1909 women according to risk category. The mean age at entry was 40 years (range, 19 to 72). Within the group of 358 carriers of pathogenic mutations, 276 had a BRCA1 mutation, 77 had a BRCA2 mutation, 1 had both a BRCA1 and a BRCA2 mutation, 2 had a PTEN mutation, and 2 had a TP53 mutation.

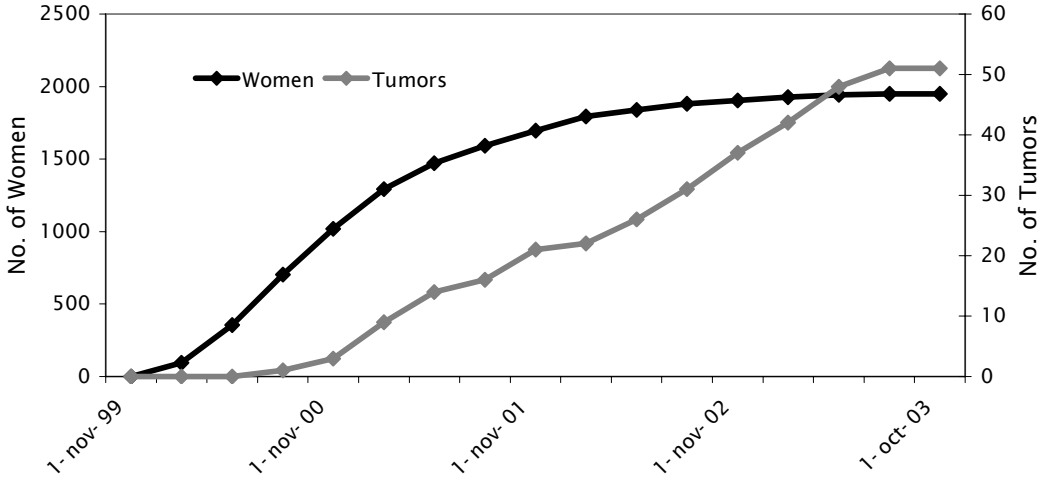

Figure 1. Women at increased risk for breast cancer enrolled and tumors detected. A total of 1952 women were enrolled, of whom 1909 were eligible for this analysis.

Breast cancers

From November 1, 1999, to October 1, 2003, 51 malignant tumors (44 invasive breast cancers, 6 ductal carcinomas in situ, and 1 non-Hodgkin's lymphoma) were detected (Figure 1), during a median follow-up period of 2.9 years (mean 2.7, range, 0.1 to 3.9 years); 1 lobular carcinoma in situ was also found. Table 2 shows the detection rate for the whole group and separately for the different risk groups. The overall rate of detection for all breast cancers (invasive plus in situ) was 9.5 per 1000 woman years at risk (95 percent confidence interval, 7.1 to 12.3), with the highest rate (26.5 per 1000) in the group of women who were carriers of the BRCA1, BRCA2, PTEN, and TP53 mutations.

Performance of the screening methods

Table 3 shows the results with the three screening methods. Of the 50 breast cancers that were detected, 5 were excluded from the analysis (Table 3). The 45 cancers that were evaluated in the comparison of the methods included 4 interval cancers (i.e., cancers detected between two episodes of screening). The first was symptomatic (30 mm in diameter, node-negative),

Table 1. Characteristics of participating women at study entry, according to risk group.*

Characteristics	Mutation Carriers (N=358)	High-Risk Group (N=1052)	Moderate-Risk Group (N=499)	Total (N=1909)
Mean age— (yr)†	38	41	40	40
Previous screening— no. (%)				
No screening	56 (16)	161 (16)	72 (15)	289 (15)
Only CBE	10 (3)	17 (2)	13 (3)	40 (2)
Imaging (with or without CBE)				
≤ 1 yr before entry	189 (53)	543 (52)	268 (54)	1000 (53)
>1-2 yr before entry	79 (22)	259 (25)	111 (22)	449 (24)
>2 yr before entry	17 (5)	46 (4)	23 (5)	86 (5)
Time unknown	2 (1)	8 (1)	4 (1)	14 (1)
Unknown	5	18	8	31
Menopausal status— no. (%)†				
Pre-menopausal	244 (72)	754 (76)	376 (78)	1365 (75)
Peri-menopausal‡	5 (2)	34 (3)	15 (3)	54 (3)
Post-menopausal	20 (6)	121 (12)	52 (11)	193 (11)
Post-menopausal after oophorectomy	66 (19)	42 (4)	12 (3)	120 (7)
Posthysterectomy	3 (1)	48 (5)	24 (5)	75 (4)
Unknown	20	53	29	102
Hormonal contraceptive use—no. (%)				
Never	40 (12)	108 (11)	45 (10)	193 (10)
Past	167 (50)	567 (56)	276 (58)	1010 (56)
Present	128 (38)	329 (33)	154 (32)	611 (34)
Unknown	23	48	24	95
HRT use—no. (%)$				
Never	291 (87)	932 (92)	436 (92)	1659 (90)
Past	19 (6)	44 (4)	19 (4)	82 (5)
Present	25 (7)	38 (4)	19 (4)	82 (5)
Unknown	23	38	25	86
Oophorectomy—no. (%)†				
No	276 (78)	1000 (96)	477 (97)	1753 (93)
Yes	77 (22)	41 (4)	13 (3)	131 (7)
Unknown	5	11	9	25

*Women in the group with mutations were those with *BRCA1*, *BRCA2*, *PTEN*, or *TP53* genetic mutations. Women in the high-risk group were those with a cumulative lifetime risk of 30 to 49 percent. Women in the moderate-risk group were those with a cumulative lifetime risk of 15 to 29 percent. CBE denotes clinical breast examination and HRT hormone-replacement therapy. Percentages are based on the numbers of women with known data; numbers with missing data are also shown.

†P<0.001 for the difference among the three groups.

‡Peri-menopausal status was defined by the occurrence of the last menstruation between 2 and 12 months before entry into the study.

$P=0.04 for the difference among the three groups.

detected seven months after screening by imaging and clinical breast examination and one month after screening by clinical breast examination only. The second (4 mm, node-negative) was detected in a specimen from a prophylactic mastectomy. The third was symptomatic (45 mm, node-negative) and was detected seven months after screening by imaging; the fourth, also symptomatic (13 mm, with isolated tumor cells in a lymph node), was detected three months after screening by imaging.

Overall, 32 breast cancers were found by MRI (22 of these were not visible on mammography), whereas 13 were missed by MRI (8 of the 13 were visible on mammography, including 5 ductal carcinomas in situ; 4 were interval cancers; and 1 tumor was detected only by clinical breast examination). In this group of 45 breast cancers, mammographic screening detected 18 tumors (10 of these were visible by MRI) and missed 27 tumors (including the 22 that were visible on MRI, the 4 interval cancers, and the 1 that was detected only by clinical breast examination).

Table 2. Detection of cases of breast cancer (including ductal carcinoma in situ) according to risk group.

Risk Group	No. of Women	Women-Years at Risk	No. of Cases Detected by Screening		No. of Cases Detected between Screenings		Rate of Detection (95% CI)*	
			Total	Invasive	Total	Invasive	All Cancers	Invasive Cancers
							no./1000	
Mutation carriers	358	867	19	16	4	4	26.5 (15.3-39.4)	23.1 (14.1-35.6)
High-risk group	1052	2968	15	15	1	1	5.4 (3.1-8.8)	5.4 (3.1-8.8)
Moderate-risk group	499	1414	11	8			7.8 (3.9-13.9)	5.7 (2.4-11.1)
Total	1909	5249	45	39	5	5	9.5 (7.1-12.3)	8.4 (6.1-11.3)

CI denotes confidence interval. Rates shown are per 1000 woman-years at risk.

With respect to all breast cancers (invasive and ductal carcinoma in situ), the sensitivity of clinical breast examination, mammography, and MRI was 17.8 percent, 40.0 percent, and 71.1 percent, respectively, when the BI-RADS score was 3 or higher (Table 3). For invasive cancers only, the respective percentages were 17.9 percent, 33.3 percent, and 79.5 percent. The specificity was 98.1 percent for clinical breast examination, 95.0 percent for mammography, and 89.8 percent for MRI.

Of the 41 cancers found by screening, 22 were detected at the first imaging screening in the study; of the women in whom cancer was detected, 16 had undergone mammographic screening before the start of the study. Two of the interval cancers were detected after the first imaging screening, and two others after a subsequent imaging screening. The sensitivity of mammography was 37.5 percent for the first screening and 42.9 percent for subsequent screening (P=0.71). The sensitivity of MRI was 79.2 percent for the first screening and 61.9 percent for subsequent screening (P=0.20).

Among the 83 clinical breast examinations with findings that were judged as probably benign or suspicious, or highly suggestive of cancer, 8 cases of malignant disease were confirmed,

Table 3. Sensitivity, specificity, and positive predictive value (PPV) of the three screening methods.*

Screening Method and BI-RADS Cutoff	No. of Tests	No. of Breast Cancers	Cumulative No. of Tests	Cumulative No. of True Positive Results	Sensitivity (%)		Specificity (%)	PPV (%)%	No. of Biopsies performed n
					Any Breast Cancer	Invasive Breast Cancer			
Clinical breast examination									
Suspicious	6	3	6	3	6.7	7.7	99.9	50.0	4
Probably benign	77	5	83	8	17.8	17.9	98.1	9.6	8
Negative	3862	37	3945	45	100	100	0	1.1	55
Mammography									
5 (highly suggestive)	3	3	3	3	6.7	7.7	100	100	3
4 (suspicious)	20	8	23	11	24.4	20.5	99.7	47.8	8
0 (need additional imaging)	32	4	55	15	33.3	28.2	99.0	27.3	9
3 (probably benign)	170	3	225	18	40.0	33.3	95.0	8.0	5
2 (benign)	240	2	465	20	44.4	38.5	89.2	4.3	4
1 (negative)	3704	25	4169	45	100	100	0	1.1	38
MRI									
5 (highly suggestive)	10	6	10	6	13.3	15.4	99.9	60.0	7
4 (suspicious)	55	15	65	21	46.6	51.3	98.9	32.3	22
0 (need additional imaging)	112	8	177	29	64.4	71.8	96.4	16.4	15
3 (probably benign)	275	3	452	32	71.1	79.5	89.8	7.1	12
2 (benign)	383	1	835	33	73.3	82.1	80.6	4.0	0
1 (negative)	3334	12	4169	45	100	100	0	1.1	11

*The results have been calculated on the basis of data on 45 of the 50 cancers. The reasons that five cases were omitted are as follows. In three cases, neither MRI nor mammography was performed (in two of these cases the women became pregnant, and in one case the woman refused MRI). In the fourth case, a tumor was detected on an additional mammogram, after a screening mammogram had been classified as Breast Imaging Reporting and Data System (BI-RADS) 0, but at a different location from the first lesion. The fifth cancer was detected at a screening visit that consisted of only a clinical breast examination. The cumulative number of true positive result is the number of cancers found at a specific BI-RADS level or higher; sensitivity is the percentage of cancers with a positive test result at a specific BI-RADS level or higher (the cumulative number of true positive results divided by total number of cancers); specificity is the percentage of negative test results in women without a cancer; PPV is the percentage of true positive test results in women who ultimately appeared to have cancer, at a specific BI-RADS level or higher (the cumulative number of true positive test results divided by the cumulative number of tests).

for a positive predictive value of 9.6 percent (Table 3). Among the 225 mammograms with findings categorized as BI-RADS 3 or higher, 18 cases of malignant disease were confirmed, for a positive predictive value of 8.0 percent. A total of 32 cancers were confirmed among 452 MRI screenings with such findings, for a positive predictive value of 7.1 percent (Table 3). With a cutoff level of BI-RADS 4, the sensitivity for both imaging methods decreased, whereas the specificity increased.

To evaluate the discriminating capacity of the imaging methods, we generated ROC curves (Figure 2). The area under the curve was 0.686 for mammography and 0.827 for MRI; the difference between the areas was 0.141 (95 percent confidence interval, 0.020 to 0.262; $P<0.05$).

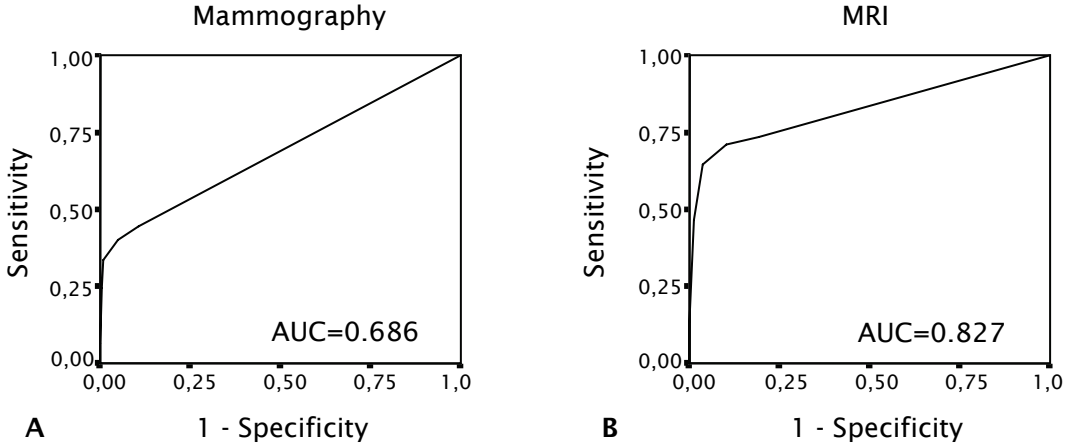

Figure 2. Receiver-operating-characteristic curves for mammography and MRI.
The difference between the area under the curve (AUC) for mammography and the AUC for MRI was 0.141 (95 percent confidence interval, 0.020-0.262; $P<0.05$).

Additional investigations

Ultrasonography was performed 889 times in 627 different women according to the protocol. Fine-needle aspiration was carried out 312 times: 267 times in combination with ultrasonography and 45 times with palpation. Biopsy was performed 85 times in 82 women and showed malignant disease in 50 cases and 1 lobular carcinoma in situ, making the rate of positive histologic findings 60.0 percent. Sixty-seven of these 85 biopsies were performed after a screening visit at which both MRI and mammography were performed. Of the 25 biopsies in women who had mammographic findings with a score of 3 or higher, 7 (28.0 percent) showed no cancer. Of the 56 biopsies in women who had MRI findings with a score of 3 or higher, 24 (42.9 percent) showed no cancer (Table 3). One of the 51 tumors was found in a specimen from a prophylactic mastectomy.

Tumor characteristics

Table 4 compares the characteristics of tumors found in the study group with those of tumors in the two age-matched control groups. In the study group, 19 of the 44 women with an invasive breast cancer (43.2 percent) had a small tumor (≤10 mm in diameter) — a proportion

Table 4. Characteristics of women with breast cancers detected in the three risk groups and in the two control groups.*

Characteristic	Mutation Carriers†	High-Risk Group	Moderate-Risk Group	Total Screened	Control Group 1 (National Cancer Registry)	Control Group 2 (Prospective Study)
No. of women	23	16	11	50	1500	45
			Number of cancers (percent)			
Age at diagnosis						
20-29 yr	2 (8.7)	0	-(-)	2 (4.0)	60 (4.0)	3 (6.7)
30-39 yr	13 (56.5)	5 (31.3)	1 (9.1)	19 (38.0)	570 (38.0)	13 (28.9)
40-49 yr	6 (26.1)	7 (43.7)	7 (63.6)	20 (40.0)	600 (40.0)	21 (46.6)
0-69 yr	2 (8.7)	4 (25.0)	3 (7.3)	9 (18.0)	270 (18.0)	8 (17.8)
Tumor size						
Dutal carcinoma in situ	3 (13.0)	0	3 (27.3)	6 (12.0)	120 (8.0)	-
Invasive tumors						
<1cm	7 (35.0)	8 (50.0)	4 (50.0)	19 (43.2)‡$	193 (14.0)	5 (12.5)
1-2 cm	6 (20.0)	5 (31.2)	3 (37.5)	14 (31.8)	508 (36.8)	15 (40.0)
>2 cm	7 (35.0)	3 (18.8)	1 (12.5)	11 (25.0)	69 (49.2)	19 (47.5)
Nodal status¶						
Negative	12 (63.2)	9 (60.0)	7 (87.5)	28 (66.7)‡‖	657 (47.6)	17 (43.6)
Isolated cells	3 (15.8)	2 (13.3)	-	5 (11.9)	-	-
Positive	2 (10.5)	3 (20.0)	1 (2.5)	6 (14.3)	723 (52.4)	22 (56.4)
Micro metastasis (0.2-2.0 mm)	2 (10.5)	1 (6.7)	-	3 (7.1)	-	-
Histologic type						
Ductal	14 (70.0)	11 (68.7)	5 (62.5)	30 (68.2)	1146 (83.0)	-
Lobular	1 (5.0)	1 (6.3)	2 (15.0)	4 (9.1)	128 (9.3)	-
Tubular	1 (5.0)	2 (12.4)	1 (12.5)	4 (9.1)	34 (2.6)	-
Medullary	4 (20.0)	1 (6.3)	0	5 (11.3)	25 (1.8)	-
Adenoid cystic	0	1 (6.3)	0	1 (2.3)	1 (0.0)	-
Other	0	0	0	0	46 (3.3)	-
Histologic grade**						
Grade 1	2 (10.5)	11 (68.8)	6 (75.0)	19 (44.2)‡††	99 (11.0)	4 (10.8)
Grade 2	5 (26.3)	1 (6.2)	2 (25.0)	8 (18.6)	339 (37.7)	14 (37.8)
Grade 3	12 (63.2)	4 (25.0)	0	16 (37.2)	462 (51.3)	19 (51.4)
Estrogen-receptor status**						
Positive	6 (33.3)	11 (73.3)	7 (87.50	24 (58.5)	-	20 (60.6)
Negative	12 (66.7)	4 (26.7)	1 (12.5)	17 (41.5)	-	13 (39.4)
Progesterone-receptor status**						
Positive	7 (36.8)	11 (73.3)	7 (87.5)	25 (59.5)	-	14 (46.7)
Negative	12 (63.2)	4 (26.7)	1 (12.5)	17 (40.5)	-	16 (53.3)

*Percentages are based on the numbers of woman with known data; numbers with missing data are not shown. In the control groups, zero denotes none, and the dash denotes not analyzed.

† There were 16 *BRCA-1*-related tumors (including 1 ductal carcinoma in situ), 6 *BRCA-2*-related tumors (including 1 ductal carcinoma in situ), and 1 *PTEN*-related tumor (ductal carcinoma in situ)

‡P<0.001 for the comparison with the National Cancer Registry control group.

$ P=0.04 for the comparison with control group 2.

¶ Nodal biopsy was not performed in two cases in the study group.

‖ P=0.001 for the comparison with control group 2.

**Histologic status was unknown in some cases in the study group.

†† P=0.01 for the comparison with control group 2.

that was significantly higher than that in the first control group (14.0 percent, P<0.001) or the second control group (12.5 percent, P=0.04). Six of 42 invasive tumors (14.3 percent) with known axillary status in the study group were node-positive and 3 (7.1 percent) had micrometastases (combined total, 21.4 percent). This rate was significantly lower than those in both control groups, in which the rates of node-positive cancer were 52.4 percent (P<0.001) and 56.4 percent (P=0.001), respectively. There were no major differences between the study and control groups with respect to histologic features, with the exception of a relatively high incidence of the medullary type in the study group (11.3 percent, vs. 1.8 percent in the first control group). In the study group, a high proportion of grade 1 tumors were in women at high risk (68.8 percent) or moderate risk (75.0 percent); however, the group of women with BRCA1, BRCA2, or other mutations had a high percentage of grade 3 tumors (63.2 percent), in addition to a high percentage of tumors that were negative for steroid receptors (Table 4).

Disease-free and overall survival

In the study group, none of the 50 patients with breast cancer (44 with invasive cancer and 6 with ductal carcinoma in situ) died before the end of the study period; the total follow-up after diagnosis was 87.6 woman-years for these 50 patients (median, 1.5 years). Contralateral breast cancer occurred in one patient. The patient with non-Hodgkin's lymphoma died.

DISCUSSION

In this prospective study, we compared the efficacy of mammographic and MRI screening for breast cancer in women with a family history of the disease or a genetic predisposition to breast cancer. Among the women examined by both methods at the same screening visit, we detected 45 breast cancers (including 6 ductal carcinomas in situ): 32 by MRI (sensitivity, 71.1 percent) and 18 by mammography (40.0 percent); five other patients were excluded from this comparison for various reasons (Table 3). Thus, the sensitivity of MRI was higher than that of mammography, but both the specificity and positive predictive value of MRI were lower.

In our sensitivity and specificity calculations, we defined lesions that were in BI-RADS category 3 and higher as positive, but most other authors have included in their calculations only lesions in BI-RADS categories 4 and 5 as positive.[21,33,34] If we had followed that policy, the sensitivity would have been 24.4 percent for mammography and 46.6 percent for MRI, in accord with the higher sensitivity previously reported for MRI.[21,33,35,36] However, the previous studies enrolled small groups of women, included some retrospective data,[35] evaluated heterogeneous groups that included women with previous breast cancers,[21,33,36] or had a plan for follow-up after a suspicious finding on MRI that differed from the follow-up plan for a suspicious mammographic finding.[33] All these factors might have artificially increased the sensitivity of MRI. We also investigated sensitivity in relation to specificity as determined by ROC curves, showing that the area under the curve was significantly higher for MRI than for mammography; this means that MRI screening could better discriminate between malignant and benign cases.

When we included only invasive breast cancers, the difference between the sensitivity of the MRI and mammography (79.5 percent vs. 33.3 percent) was even greater than the difference overall (71.1 percent vs. 40.0 percent). MRI detected 20 cancers (including 1 ductal carcinoma in situ) that were not found by mammography or clinical breast examination. The stage of these 20 cancers was favorable; 11 of the 19 invasive tumors were smaller than 10 mm, and only 1 was associated with a positive node.

Another important matter that we addressed was the best method for detecting carcinoma in situ. Our study showed that mammography had a higher sensitivity than MRI for detecting ductal carcinoma in situ: 83 percent (five out of six cancers detected), as compared with 17 percent (one out of six) for MRI (P=0.22).

To investigate whether screening improves the chance of diagnosing breast cancer at an early stage, we compared the distribution of tumor stages in our study with the distribution in two external control groups. The first group consisted of age-matched women in a database of all breast cancers diagnosed in 1998 in the Netherlands. A drawback of this group is that we had no information about whether or not they had been screened or the family history. Therefore, we added a second control group from a prospective population-based study of the prevalence of mutations in patients with breast cancer. From this group, we selected all patients with an age and a family history of breast cancer that were similar to the women in our surveillance study. The tumors in our study group were significantly smaller and were less likely to be node-positive than those in the two control groups. Most screening studies (without MRI) in high risk women have shown a higher incidence of positive nodes (30 to 45 percent) than we found (21 percent).[17,18,37] Moreover, Kollias et al.[38] found no significant differences in the size or grade of invasive tumors or in lymph-node status between women who had symptoms of cancer and women whose cancers had been found on screening by mammography. So we may conclude that MRI screening did indeed contribute to the early detection of hereditary breast cancer.

However, larger tumors (>2 cm in diameter) were found more often in the women with BRCA1, BRCA2, PTEN, and TP53 mutations than in the other two risk groups in our study, suggesting that more frequent screening is needed for women with these mutations. A drawback of MRI screening is that it has a lower specificity than mammography, and as a result, MRI will generate more findings judged as uncertain, which require short-term follow-up or additional investigations.[39] In our study, screening by MRI led to twice as many unneeded additional examinations as did mammography (420 vs. 207) and three times as many unneeded biopsies (24 vs. 7).

In conclusion, our study shows that the screening program we used, especially MRI screening, can detect breast cancer at an early stage in women at risk for breast cancer.

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Appendix

In addition to the authors, the following investigators participated in the MRISC Study: Erasmus Medical Center, Rotterdam - C.C.M. Bartels, A. Ciurea, A.N. van Geel, E.J. Meijers-Heijboer, M. Menke, A.J. Rijnsburger, C. Seynaeve, D. Urich; Leiden University Medical Center, Leiden - C. van Asperen, M.N.J.M. Wasser; Netherlands Cancer Institute, Amsterdam - R. Kaas, W. Koops, M. Piek-den Hartog, M. van de Vijver; University Hospital Groningen, Groningen - C. Dorbritz, S. van Hoof, A.M. van der Vliet, J. de Vries; University Medical Center Nijmegen, Nijmegen - J.O. Barentsz, H. Brunner, J.H.C.L. Hendriks, R. Holland, N. Hoogerbrugge, M. Stoutjesdijk, A.L.M. Verbeek, T. Wobbes; Free University Medical Center, Amsterdam - F. Menko, A. Taets van Amerongen.

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CHAPTER 5

Differences between first and subsequent rounds of the MRISC breast cancer screening program for women with a familial or genetic predisposition

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Abstract

Background Within the Dutch MRI Screening (MRISC) study, a Dutch multicenter screening study for hereditary breast cancer, the authors investigated whether previously reported increased diagnostic accuracy of magnetic resonance imaging (MRI) compared with mammography would be maintained during subsequent screening rounds.

Methods From November 1999 to October 2003, 1909 eligible women were included in the study. Screening parameters and tumor characteristics of different rounds were calculated and compared. The authors defined 3 different types of imaging screening rounds: first round in women never screened by imaging before, first round in women screened by imaging (mainly mammography) before, and subsequent rounds.

Results The difference in sensitivity for invasive cancers between mammography and MRI was largest in the first round of women previously screened with mammography (20.0 vs. 93.3%; P = .003), but also in subsequent rounds, there was a significant difference in favor of MRI (29.4 vs. 76.5%; P = .02). The difference in false-positive rate between mammography and MRI was also largest in the first round of women previously screened with mammography (5.5 vs. 14.0%; P<.001), and it remained significant in subsequent rounds (4.6 vs. 8.2%; P<.001). Screen-detected tumors were smaller and more often lymph node negative than symptomatic tumors in age-matched control patients, but no major differences in tumor stage were found between tumors detected at subsequent rounds compared with those in the first round.

Conclusions In subsequent rounds, a significantly higher sensitivity and better discriminating capacity of MRI compared with mammography was maintained, and a favorable tumor stage compared with age-matched symptomatic controls. As results of these subsequent screening rounds were most predictive for long-term effects, the authors expect that this screening program will contribute to a decrease of breast cancer mortality in these high-risk women.

INTRODUCTION

In western countries, women with a familial or genetic predisposition for breast cancer often opt for either prophylactic surgery or intensive surveillance,[1,2] which frequently starts between the ages of 25-35 years. Screening in this group usually consists of mammography and clinical breast examination (CBE),[3,4] but the effectiveness of breast cancer screening with these modalities is questionable, especially in carriers of a BRCA1/2 germline mutation.[2,4] Recently, retrospective and prospective magnetic resonance imaging (MRI) screening studies were started to investigate whether MRI is a better screening method in this high risk group of women.[5,6] The study design[7] and the first results of the Dutch multicenter prospective study for MRI screening in women with a familial or genetic predisposition (MRISC study) have been reported.[8] Participants were screened for breast cancer by a 6-month complete breast examination (CBE) in addition to yearly mammography and MRI examinations, which were independently evaluated. We found that screening facilitated breast cancer diagnosis at an earlier tumor stage in these study participants than in symptomatic age-matched controls and that MRI was more sensitive, but less specific, than mammography. Overall, the sensitivity of mammography for invasive cancers was 33% and that of MRI 80%. The false-positive rate was 5% for mammography and 10% for MRI. However, it is known that screening parameters and tumor characteristics can differ among different rounds of a screening program, especially when the first round is compared with subsequent rounds, looking for prevalent and incident tumors, respectively. In the first round, the effect of length-time bias, caused by slowly growing cancers that have a longer detectable preclinical phase, is higher than in subsequent rounds.[9] This may result in a higher detection rate and a higher percentage of large tumors at the first screening round in comparison with subsequent rounds.[10,11] On the other hand, the availability of previous examinations at subsequent imaging rounds can decrease the recall rate in comparison with the first round.[12] It has to be noted that in the MRISC[8] study and other MRI screening studies,[13-16] MRI was added to the existing screening program of mammography and CBE in a significant number of the high-risk women. This means that results of the first screening round in these studies were frequently based on comparing a first MRI with a subsequent mammography. It could be that mammographically occult cancers were preferentially detected by MRI in the first screening round of women previously screened with mammography, which might exaggerate the difference in performance between MRI and mammography. Therefore, it is important to investigate whether this initially large difference between mammography and MRI is maintained in subsequent screening rounds. This analysis was performed by comparing the percentage of positive tests and the positive predictive value (PPV) of the 3 different screening modalities between each of the different rounds. Furthermore, we compared the detection rate and screening parameters of mammography and MRI from the first imaging round of women who had never been screened by mammography with those of the first imaging round of women who had been screened by mammography and with those of subsequent imaging rounds. Finally, tumor characteristics of cancers detected during first and subsequent rounds were compared.

MATERIALS AND METHODS

The design and methods of the MRISC study have been previously described.[7,8] In brief, from November 1999 until October 2003, 1952 women with a genetic breast cancer risk from 6 different centers in the Netherlands were included. All participating women gave written informed consent. Inclusion criteria were a cumulative lifetime risk of breast cancer from ≥15% because of a genetic (358 proven gene mutation carriers) or familial predisposition according to the modified tables of Claus,[17] an age at entry between 25 and 70 years, and no evident symptoms suspicious for breast cancer or previous breast cancer. From the 1952 women initially included, 1909 women were eligible for this study's analyses, with a median follow-up of 2.9 years. In this group of 1909 women, 50 breast cancers were detected, including 6 cases of ductal carcinoma in situ (DCIS). The overall detection rate was 9.5 per 1000 women years, and for invasive cancers it was 8.4 per 1000 women years.

Participating women were screened twice a year by CBE in addition to mammography and MRI once a year, which were independently evaluated. The mammography and MRI were scored in a standardized way according to the Breast Imaging Reporting and Data System (BI-RADS).[18,19] We defined a BI-RADS Score 3 ("probably benign finding"), Score 0 ("need additional imaging evaluation"), Score 4 ("suspicious abnormality"), or Score 5 ("highly suggestive of malignancy") as positive, because, in these cases, additional examination was indicated.

In general, screening rounds occurred every 6 months in view of biannual CBE. Imaging screening rounds by MRI and mammography occurred yearly. For every general screening round, the number of CBEs, mammographies, and MRIs performed were counted. For each of the 3 screening modalities, the percentage of positive tests, the breast cancer detection rate per 1000 tests and the positive predictive value (PPV) were calculated per screening round. The PPV was calculated as the number of positive test results in women who ultimately appeared to have cancer divided by the total number of positive tests.

To compare the detection rate of invasive cancers and the screening parameters of both mammography and MRI in the first and subsequent imaging rounds, we distinguished 3 types of imaging screening rounds,

1. First imaging round in women never screened before by neither mammography nor MRI (referred to as "without prior mammography"),
2. First imaging round in women already screened before the start of the study by mammography (referred to as "with prior mammography"), and
3. Subsequent rounds.

For comparison of screening parameters between these 3 types of screening rounds, we used only the screening rounds that included the results of both mammography and MRI. Therefore, numbers do not necessarily total 1909. The analyses for comparison of true positive rate and false-positive rate between the first imaging round without prior mammography, the first imaging round with prior mammography, and subsequent rounds were based on only invasive cancers, because there was a difference between the sensitivity of MRI for invasive breast cancers and DCIS[8] and because the numbers of DCIS were too small

for a separate statistical analysis. For subsequent rounds, receiver operating characteristic (ROC) curves were constructed for mammography and MRI.

Characteristics of tumors detected during the different imaging screening rounds were described and compared. To determine whether breast cancers detected at or in the interval after a subsequent screening round were diagnosed at a more favorable stage, tumor characteristics of this subgroup of breast cancers were separately compared with those from 2 symptomatic control groups, earlier described and used in our previous article.[8] The first control group was derived from all breast cancers diagnosed in 1998 in the Netherlands, where data were obtained from the National Cancer Registry. Subjects were matched for age at diagnosis with patients from the MRISC study group (in 5-year categories). The second group comprised unselected patients, who were diagnosed in Leiden and Rotterdam with primary breast cancer between 1996 and 2002 and who were participating in a prospective study ("PROSPECT STUDY") to investigate the prevalence of gene mutations. From this series of consecutive patients, we selected non-screened patients who were between 25 and 60 years old with a cumulative lifetime risk of ≥15% for breast cancer due to a family history, which was routinely recorded in this database.

Statistics

Differences in percentage of positive tests, detection rate, and PPV between general screening rounds were tested by a chi-square test (linear-by-linear association). Differences in results of screening parameters among the 3 types of imaging screening rounds (the first round without prior mammography, the first round with prior mammography, and subsequent rounds) were tested by a Pearson chi-square test, and differences between mammography and MRI were tested by an MC Nemar chi-square test. The area under the curve (AUC) of the ROC curves (a measure for discriminative capacity of a diagnostic test) for mammography and MRI were compared and tested by a z-test. Differences in tumor characteristics among the 3 types of screening rounds were tested by a Pearson chi-square test; differences in these characteristics of screen-detected tumors during subsequent rounds versus those of the symptomatic control groups were tested by a Fisher exact test. A two-sided P value of $<.05$ was considered to indicate statistical significance. All statistical analyses were performed by SPSS (version 9.0, SPSS Inc, Chicago, IL).

RESULTS

In Table 1 the number of tests, percentage of positive tests, breast cancer detection rate, and the positive predictive value (PPV) per general screening round are presented for all 3 different screening modalities. In view of the screening scheme, nearly all women had a CBE at the first screening round, whereas the first mammography and MRI were especially performed during either the first or the second general screening round with an interval of 6 months between rounds. At the first round, the percentage of positive tests was 3.0, 6.7, and 12.9% for CBE, mammography, and MRI, respectively. For CBE, there was no significant change in percentage of positive tests, detection rate, and PPV during subsequent rounds. At

Table 1. Number of tests and all detected breast cancers (invasive + DCIS) per general screening round*.

	CBE				Mammography				MRI			
No. of general round*	Tests n	Positive Tests n (%)	Detected BC n (per 1000 tests)	PPV (%)	Tests n	Positive Tests n (%)	Detected BC n (per 1000 tests)	PPV (%)	Tests n	Positive Tests n (%)	Detected BC n (per 1000 tests)	PPV (%)
1st round	1878	57 (3.0)	1 (0.5)	1.8	1150	77 (6.7)	7 (6.1)	9.1	1042	134 (12.9)	10 (9.6)	7.5
2nd round	1717	54 (3.1)	4 (2.3)	7.4	857	41 (4.8)	3 (3.5)	7.3	826	93 (11.3)	10 (12.1)	10.8
3rd round	1528	47 (3.1)	3 (2.0)	6.4	940	52 (5.5)	5 (5.3)	9.6	900	114 (12.7)	6 (6.7)	5.3
4th round	1271	26 (2.0)	1 (0.8)	3.8	619	23 (3.7)	2 (3.2)	8.7	583	54 (9.3)	2 (3.4)	3.7
5th + next rounds	2033	56 (2.8)	2 (1.0)	3.6	1049	58 (5.5)	2 (1.9)	3.4	958	66 (6.9)	4 (4.1)	6.1
P		.25	.87	.94		.16	.15	.29		<.001	.009	.30

DCIS: ductal carcinoma in situ; CBE: clinical breast examination; MRI: magnetic resonance imaging BC: breast cancer ;and PPV: positive predictive value.

*The interval between 2 general screening rounds is 6 months in view of bi-annual CBE. At the first and subsequent general screening rounds women can be screened only by CBE without an imaging technique. Not always women received all three screen modalities together, thus numbers does not necessarily add up to 1909.

the first 2 general rounds (i.e., 1 imaging round) the percentage of positive tests by MRI (12.9 and 11.3%) was at least twice as high compared with mammography (6.7% and 4.8%). However, during subsequent rounds, the percentage of positive tests by MRI decreased significantly (P<.001) from 12.9 to 6.9%, whereas for mammography, no significant differences during follow-up were observed (P = .16). With respect to the breast cancer detection rate, there was a statistically non-significant trend toward a decrease for mammography and a statistically significant (P = .009) decrease for MRI, especially from the fourth general round. The PPV did not show a significant decrease during subsequent rounds for either MRI (P = .30) or mammography (P = .29).

In Table 2, the screening parameters of mammography and MRI for invasive cancers in the 3 types of imaging screening rounds (first round of women without prior mammography, first round of women with prior mammography, and subsequent rounds) are presented. As described in Materials and Methods for this analysis, we selected only rounds in which both mammography and MRI were performed. As a consequence, apart from 6 DCIS, 5 invasive breast cancers were excluded from the analysis (see footnote Table 2). Of 1723 evaluable women, 303 (18%) women were never previously screened by mammography and MRI before the study, and 1420 (82%) women had already been screened by mammography before entry in the study.

For mammography, the detection rate of invasive cancers was 16.5 per 1000 tests in the first imaging round in women without prior mammography, which was significantly (P = .003) higher than in the first screening round in women with prior mammography (2.1 per 1000 tests) and in subsequent rounds (2.1 per 1000 tests). For MRI, the detection rate of invasive cancers was also highest in the first round in women without prior mammography (13.2 per 1000 tests), but it was also high in the first round in women with prior mammography (9.9 per 1000 tests) compared with the detection rate in subsequent rounds (5.3 per 1000 tests) resulting in a significant trend. Similar results for mammography and MRI were found for the PPV (Table 2). There was no large difference between the true-positive rate (sensitivity) of mammography (5 of 7) and MRI (4 of 7) for invasive breast cancers in the first round in women without prior mammography (71.4 vs. 57.1%). The difference in sensitivity between mammography and MRI was largest in the first imaging round with prior mammography, i.e., 20.0% (3/15) vs. 93.3% (14 of 15) (P =.003). Moreover, also in subsequent rounds, this difference remained significant for invasive tumors (29.4 vs. 76.5%; P=.02). The difference in false-positive rate (1-specificity) between mammography and MRI was largest in the first imaging round in women with prior mammography (5.5 vs. 14.0%; P<.001) in favor of mammography. For subsequent rounds, the false-positive rate also remained lower for mammography than for MRI (4.6 vs. 8.2%; P<.001).

The area under the curve (AUC) in the receiver operating characteristic (ROC) curves for subsequent rounds was 0.665 for mammography and 0.850 for MRI (Figure 1). The difference between the areas was 0.185 (95% confidence interval [CI] 0.003-0.367); P<.05).

The characteristics of 45 evaluable tumors (the 6 DCIS are separately indicated) detected in the 3 different kinds of imaging screening rounds (including 4 interval cancers) are presented in Table 3 in comparison with those of the 2 symptomatic control groups. In total, 22

Table 2. Screening parameters for first and subsequent imaging rounds regarding 39 evaluable invasive breast cancers.*

	No. of Tests	No. of Positive Tests n (%)	No. of True Positives	No. of False Negatives	Detection Rate per 1000 Tests	PPV %	True Positive Rate, Sensitivity %	False Positive Rate, 100-Specificity %
Mammography								
First imaging round, without prior mammography	303	23 (7.6)	5	2	16.5	21.7	71.4	6.1
First imaging round, with prior mammography	1420	80 (5.6)	3	12	2.1	3.8	20.0	5.5
Subsequent imaging rounds	2431	116 (4.8)	5	12	2.1	4.3	29.4	4.6
P		0.09			0.003	0.003	0.05	0.33
MRI								
First imaging round, without prior mammography	303	25 (8.3)	4	3	13.2	16.0	57.1	7.1
First imaging round, with prior mammography	1420	211 (14.9)	14	1	9.9	6.6	93.3	14.0
Subsequent imaging rounds	2431	212 (8.7)	13	4	5.3	6.1	76.5	8.2
P		<0.001			0.05	0.18	0.14	<0.001

*Based on 39 of the 44 invasive breast cancers (6 ductal carcinoma in situ (DCIS) were excluded). Reasons for omitting 5 cases: in 3 cases no magnetic resonance imaging or mammography was performed, because of pregnancy (n=2; 1 in the interval 16 months after imaging, 35 mm, micro-invasive lymph node) or refusing MRI (n=1). In the fourth case a tumor was detected by an additional mammography, after a screening mammography classified as BI-RADS "0" but a location different from the first lesion. The fifth case was detected at a screening visit consisting of only a clinical breast examination (CBE). Percentage positive tests indicates percentage of tests with a positive result (number of positive tests divided by number of tests); True positives, number of positive tests in women who appeared to have cancer; False positives, number of positive tests in women who do not appeared to have cancer; False negatives, number of negative tests in women who appeared to have cancer; Detection rate, number of tests per 1000 tests that detected a cancer (the number true positives divided by the number of tests; PPV, percentage of positive tests that were true positive (the number of true positives divided by the number of positive tests); True positive rate, percentage of cancers that had a positive test result (the number of true positives divided by the total number of cancers); False positive rate, percentage positive test results in women who did not appeared to have cancer (the number of false negatives divided by the total number of tests in women who do not appear to have cancer).

prevalent invasive breast cancers were found during the first screening round with (n = 15) or without (n = 7) prior mammography, whereas 17 invasive incident cancers were detected during subsequent screening rounds. Nine (41%) of these 22 prevalent invasive cancers were 1 cm or smaller, which was not significantly different in comparison with 53% (9 of 17) of the incident cancers (cancers found during subsequent screening periods) (P = .52). The node-negativity rate (including isolated tumor cells) was 86% (19 of 22) for prevalent cancers and 69% (11 of 16) for incident cancers (P = .24). Of the tumors detected during the first round 23% (5 of 22) had a high differentiation grade, in contrast to 47% (8 of 17) in the incident tumors (P =.10).

When comparing characteristics of screen-detected tumors with those of the control groups, especially the size of the incident tumors were more frequently (53%) ≤1 cm in comparison with both symptomatic control groups (14.0% (P<.001) and 12.5% (P =.005), respectively).

Tumors found during subsequent rounds were also, although not significantly, less likely (31.3% i.e., 5 of 16) to be lymph node positive (including micrometastasis) than those in both symptomatic control groups, where the lymph node positivity rate was 52.4% (P =.09) and 56.4% (P =.09), respectively.

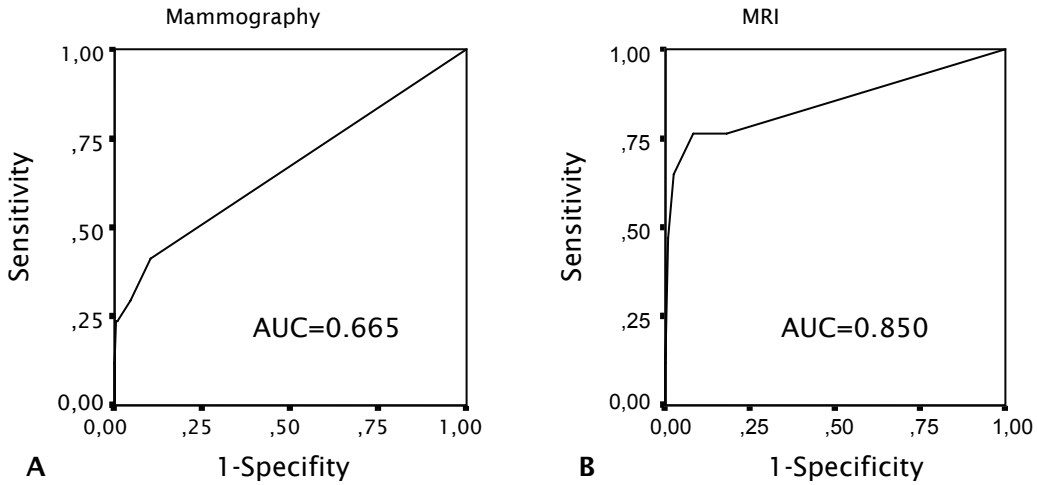

Figure 1. Receiver Operating Characteristic (ROC) curves of subsequent screening rounds for A, mammography and B, magnetic resonance imaging (MRI). The differences between the area under the curve (AUC) for mammography and MRI was 0.186 (95% confidence interval [CI], 0.003-0.367; P=.046).

DISCUSSION

In various countries, breast cancer screening for young women with a familial or genetic predisposition is a realistic option to reduce breast cancer mortality.[3] Because of the low sensitivity of mammography in this group, other venues to improve early detection are explored. For this purpose, the value of MRI as a screening method is being investigated,[5-8,13-16] for instance, in our large Dutch MRI screening study, the MRISC.[8] This study concluded that MRI was more sensitive than mammography, but less specific, and that tumor characteristics from women in the study were more favorable when compared with those of age-matched symptomatic controls.[8] However, data on screening parameters and tumor characteristics can differ between different screening rounds, especially between the first and subsequent rounds. Therefore, apart from overall results, it is also important to report results separately for the different rounds in a screening program. In the MRISC study as well as in other MRI screening studies,[13-16] MRI (and in some studies also ultrasound) was added to the already existing screening program using mammography and CBE. This means that, within this study, the result of a first MRI is compared with the result of a mammography in women with a prior mammography before start of the study. Therefore, it may be that in the first screening round in the group of women with prior mammography, mammographically occult carcinomas were preferentially detected by MRI, thus exaggerating differences in sensitivity between MRI and mammography. However, in subsequent rounds, all women had both a mammography and MRI in a prior round, resulting in less imbalance. Therefore, although the

number of tumors detected in the MRISC study was still relatively small, in this detailed study we separately analyzed screening results in these different screening rounds.

Table 3. Characteristics of detected breast cancers by imaging screening round (39 invasive BC + 6 DCIS).

	1st Imaging Round, Without Prior Mammography		1st Imaging Round, With Prior Mammography		Subsequent Rounds		Control Group 1, NCR		Control Group 2, Prospective Study	
	n	%	n	%	n	%	n	%	n	%
Total cancers	7		17		21		1500		45	
Interval cancers	1		1		2		-		-	
Tumor size										
Tis	0	0	2	11.1	4	19.0	120	8.0	-	-
T≤ 1cm	2	28.6	7	46.7	9	53.0	193	14.0	5	12.5
T 1-2 cm	4	57.1	5	33.3	4	23.5	508	36.8	15	40.0
T>2 cm	1	14.3	3	20.0	4	23.5	691	49.2	19	47.5
Nodal status										
N0	7	100	10	66.7	9	56.2	657	47.6	17	43.6
Isolated cells	0	0	2	13.3	2	12.5	-	-	-	-
N-positive	0	0	1	6.7	4	25.0	723	52.4	22	56.4
Micrometastasis (0.2-2.0 mm)	0	0	2	13.3	1	6.3	-	-	-	-
Unknown					1					
Histologic grade										
Grade I	6	85.7	8	53.3	5	29.4	99	11.0	4	10.8
Grade II	0	0	3	20.0	4	23.5	339	37.7	14	37.8
Grade III	1	14.3	4	26.7	8	47.1	462	51.3	19	51.4

BC: breast cancer; DCIS: ductal carcinoma in situ; NCR: National Cancer Registry.

We found that, for all 3 screening modalities, the positive test rates and PPV were reasonably stable over time. Only for MRI, there was a significant trend of a decreasing positive test rate over time. Apart from a higher rate of prevalent cancers, possible reasons for this latter observation are the availability of a previous MRI for comparison and more experience of radiologists in interpretation of MRI in subsequent rounds, resulting in less false-positive tests.

For mammography as well as MRI, the detection rate was indeed highest in the first round in women without a prior mammography. In contrast to mammography, for MRI the detection rate in the first imaging round in women with prior mammography was also higher than in subsequent rounds. This may be caused by the preferential detection of mammographically occult cancers by MRI in this round. Warner et al.[15] found only a slightly higher overall detection rate by MRI in the first round (46.6 per 1000 tests) compared with the second round (36.8 per 1000 tests).

Because of a small absolute number of cancers (n=7) in the first imaging round in women without prior mammography, it is not possible to draw hard conclusions about differences in sensitivity of mammography and MRI in this subgroup of women. The difference in

sensitivity between mammography and MRI was most obvious in the first imaging round in women with a prior mammography (20.0 vs. 93.3%; P=.001). Therefore, the inclusion of the large subgroup with prior mammography before start of the study probably resulted in overestimation of the difference in sensitivity between mammography and MRI. Indeed, in subsequent screening rounds, the difference in sensitivity (29.4% vs. 76.5%) decreased, but it remained significantly (P=.02) in favor of MRI. This means that also in subsequent rounds, MRI is a more sensitive method than mammography for early detection of breast cancer. Warner et al.[15] found also a higher difference in sensitivity in the first round (38% vs. 85%) compared with the second round (43% vs. 71%) (Table 4), for all breast cancers combined, although they made no differentiation between a first round in women without and with a prior mammography. They also found a slight decrease in sensitivity of MRI and a similar sensitivity of mammography in subsequent rounds. Although the percentage of women screened before their MRI study was not given in their reports,[15,20] MRI was also added to the existing screening program consisting of mammography and CBE in probably a significant number of women. Regarding the British Royal College of Radiologists MARIBS study, Leach et al.[16] found no decrease in sensitivity of MRI between the first and subsequent rounds (75% vs. 80%, respectively), while the sensitivity of mammography also remained unchanged (40% vs. 40%). However, the differences among these 3 studies are probably not significant.

Table 4. Comparisons of sensitivity and specificity of first and subsequent imaging screening rounds in 3 different studies.

	Sensitivity Mammography,%		Sensitivity MRI,%		Specificity Mammography,%		Specificity MRI,%	
	1st Round*	Subsequent Rounds	1st Round*	Subsequent Rounds	1st Round*	Subsequent Rounds	1st Round*	Subsequent Rounds
MRISC study*[8]	36	29	82	77	94	95	87	92
Canadian study[13]	38	43	85	71	99.6	100	93	97
MARIBS study[11]	40	40	75	80	93	94	82	81

MRISC: Dutch MRI screening study; MARIBS: magnetic resonance imaging for breast cancer screening study of the Royal College of Radiologists, United Kingdom.

*1st round is first round with and without prior imaging together.

As expected, for mammography, the specificity was lower in the first imaging round in women without a prior mammography than in subsequent rounds, but in both first imaging rounds together (with and without prior imaging), specificity was comparable to those in subsequent rounds (94% vs. 95%) (Table 4). For MRI, the specificity was lower in both first imaging rounds together than in subsequent rounds (87% vs. 92%) (Table 4). In the already mentioned Canadian (Warner et al.[15]) study, the same trend was seen; the specificity of MRI increased from 93% in the first round to 97% and 99% in the second and third round, respectively.[15] In the British study this trend was absent and specificity of MRI was comparable for the first and subsequent rounds (82 vs. 81%, respectively).[16] The findings in the MRISC and Canadian study are in line with findings from the Dutch nationwide breast cancer screening program for women aged 50-75 years[21] and the screening programs in the

United States.[22,23] The specificity of mammography in those studies was also lower in the first screening round than in subsequent rounds. A possible explanation of these observations is the absence of previous images during the first round for comparison,[12] but for MRI, it is also possible that radiologists involved in these studies gained experience in interpretation of this detection method during subsequent rounds, thus lowering false-positive rates.

For sensitivity, we saw the highest contrast between mammography and MRI in the first imaging round of women with prior mammography (94.5% vs. 86.0%; P<.001), but there was also a significant difference between both modalities in subsequent rounds (95.4% vs. 91.8%; P<.001). Thus, also the difference in specificity between mammography and MRI regarding the overall results may be an overestimation, because in the first round in the group of women with prior mammography, the mammography can be compared with the previous one, whereas this is not possible for the MRI.

Because results from subsequent rounds are most predictive for long-term effects, we generated ROC curves of these rounds separately. Comparison of the AUC, a measure for the discriminating capacity of a diagnostic test (including sensitivity and specificity), showed that also in subsequent rounds, MRI could better discriminate between benign and malignant cases than mammography (P =.046).

The ultimate goal of screening is to reduce the stage of breast cancer at the time when the cancer is first detected in order to reduce the breast cancer mortality. Smaller tumors in incident rounds as compared with the prevalent round are expected in screening programs through the detection of more large slowly growing tumors in the prevalent round (length-time bias).[9] In contrast with this theory, it has been reported that, in many screening studies, tumors detected in subsequent rounds are not smaller than tumors detected in the first round or that the differences are very small.[24] In our study, the characteristics of prevalent tumors found in the first round without prior mammography were suggestive of this length time bias sampling: the majority (85.7%) was Bloom and Richardson Grade 1, all were node-negative, even though there were fewer (28.6%) small tumors (≤1 cm) than in the 2 other subgroups. However, these differences in prevalent tumor characteristics were not significant when compared with those of the cancers detected during subsequent rounds. Characteristics of invasive cancers found overall,[8] and also in subsequent rounds, were more favorable with respect to tumor size, nodal status, and differentiation grade compared with tumors found in symptomatic control patient groups.

In conclusion, it is reassuring that also in subsequent rounds, a higher sensitivity and a better (P=.046) discriminating capacity (based on ROC AUCs) of MRI in comparison with mammography was found along with a favorable tumor stage compared with age-matched symptomatic controls. As results of these subsequent screening rounds are most predictive for long-term effects, we expect that this screening program will contribute to a decrease of breast cancer mortality in these high-risk women.

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CHAPTER 6

Tumor characteristics and detection method in the MRISC screening program for the early detection of hereditary breast cancer

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Abstract

In the MRISC study, women with an inherited risk for breast cancer were screened by a 6-monthly clinical breast examination and yearly MRI and mammography. We found that the MRISC screening scheme could facilitate early breast cancer diagnosis and that MRI was a more sensitive screening method than mammography, but less specific. In the current study we investigated the contribution of MRI in the early detection of breast cancer in relation to tumor characteristics.

From November 1999 to October 2003, 1909 women were included and 50 breast cancers were detected, of which 45 were evaluable and included in the current study. We compared the characteristics of tumors detected by MRI-only with those of all other (non-palpable) screen-detected tumors. Further, we compared the sensitivity of mammography and MRI within subgroups according to different tumor characteristics.

Twenty-two (49%) of the 45 breast cancers were detected by MRI and not visible at mammography, of which 20 (44%) were also not palpable (MRI-only detected tumors). MRI-only detected tumors were more often node negative than other screen-detected cancers (94 vs. 59%; p=0.02) and tended to be more often ≤1cm (58 vs. 31%; p=0.11). MRI was more sensitive than mammography for a wide spectrum of invasive tumor characteristics i.e. size, nodal status, histology, grade and ER status.

Half of the breast cancers detected in this study were visible by MRI only and these tumors were smaller and significantly more often node-negative than other screen-detected tumors, suggesting that MRI makes an important contribution to the early detection of hereditary breast cancer.

INTRODUCTION

The value of mammographic screening in women with a familial or genetic predisposition for breast cancer is currently unproven.[1-3] However, first results of four prospective MRI screening studies, in which MRI and mammography were combined in women with an increased risk of hereditary breast cancer, showed that MRI was a more sensitive screening method than mammography.[4-7] The Dutch national MRISC study is the first study that showed that the breast cancers detected in the screening group had a more favorable stage than tumors diagnosed in symptomatic age-matched controls. These results are in line with results from the Canadian, British and German study, in which tumor stages appeared to be favorable, although there was no direct comparison with a symptomatic control group.[5-7] With a computer simulation model (MISCAN) it was estimated that applying the MRISC screening scheme (including MRI) in the age group 30-50 years, in combination with the national mammography screening program from 50 until 75 years, could reduce breast cancer mortality by about 40% in BRCA1/2 gene mutation carriers. Furthermore, the MRISC screening scheme appeared to be cost-effective.[8]

Although it is clear that this screening scheme is sensitive and can lead to the detection of early-stage breast tumors, the contribution of MRI in the early detection has not exactly been quantified. Further, it might be that different subgroups of tumors are detected preferentially either by MRI or mammography. For instance, it is known from diagnostic studies that invasive lobular cancer (ILC) is more difficult to detect at mammography than invasive ductal cancer (IDC), because of the frequent low opacity in the tumor which is similar to normal fibroglandular breast tissue, a low rate of suspicious calcifications and a diffuse growth pattern.[9-11] Also, medullary cancers can mimic a benign mass at mammography, because they have often pushing borders.[12] In the Swedish two-county study of mammography screening the sensitivity for medullary cancer, IDC grade 3 and DCIS was lower than that of cancers with an other morphology.[13]

The reported sensitivity of MRI for DCIS in a diagnostic setting is variable and ranges from 40-100% (reviewed in refs 14-16). Especially low grade DCIS is more frequently associated with no contrast uptake or slow uptake of contrast and no wash out, mimicking benign tissue.[17] The few data about the sensitivity of MRI for ILC in a diagnostic setting, suggest that it might be slightly lower than that for IDC, although most lesions were visible on MRI.[18-20] Additionally, ILC as well as medullary carcinoma can demonstrate slow uptake of contrast and no wash out or no contrast uptake at all, producing a false-negative examination.[21]

Therefore we investigated the relative contributions of MRI, mammography and clinical breast examination (CBE) in the early detection of various types of hereditary breast cancer in the context of the MRISC study. The tumor characteristics of MRI-only detected tumors were compared with those of other screen-detected tumors. In addition, we investigated the sensitivity of mammography and MRI separately for different tumor characteristics.

MATERIAL AND METHODS

The MRISC study is a national, prospective, non-randomized study investigating the value of MRI screening in women with a familial or genetic predisposition for breast cancer. The design and methods have been described in detail before.[4,22] In brief: between November 1, 1999 and October 1, 2003 1909 high-risk women from 6 different academic and/or cancer centers were included. Inclusion criteria were a cumulative lifetime risk of breast cancer from ≥ 15% due to a genetic or familial predisposition according to modified tables of Claus,[22,23] age at entry between 25 and 70 years and no previous breast cancer or evident symptoms suspicious for breast cancer. Participating women were screened twice a year by CBE in addition to mammography and MRI once a year, with independent evaluation. The mammography and MRI were scored in a standardized way according to the Breast Imaging Reporting and Data System (BI-RADS).[24,25] An imaging test with BI-RADS score 3 ("probably benign finding"), O ("need additional imaging evaluation"), 4 ("suspicious abnormality") and 5 ("highly suggestive of malignancy") is defined as positive, because in these cases additional examination was indicated. A BI-RADS score of 1 ("negative") and 2 ("benign finding") were defined as negative. All the biopsy specimens that formed the basis for the diagnosis of breast cancer were reviewed by an expert pathologist.

In the 1909 participants (including 358 mutation carriers), 51 tumors were detected in the breast of which 6 cases of DCIS, 44 invasive breast cancers and 1 case of lymphoma. The median follow-up period was 2.9 years. The overall detection rate was 9.5 per 1000 women years, which for invasive cancers was 8.4 per 1000 women years.

In the current study, the detection method or combination of detection methods of the 50 breast cancers detected in the MRISC study was investigated. Further, the tumor characteristics were studied separately for each detection method. Characteristics of the tumors detected by MRI and missed by mammography and palpation (referred to as 'MRI-only detected tumors') were compared with two groups of other screen-detected tumors, being:

1) All palpable and non-palpable screen-detected tumors (except the MRI-only detected tumors) referred to as 'all other screen-detected tumors'.

2) Non-palpable screen-detected tumors (except the MRI-only detected tumors) i.e. tumors detected by mammography only and tumors detected by both mammography and MRI, referred to as 'non-palpable other screen-detected tumors'.

Differences between characteristics of MRI-only detected tumors and both comparison groups were tested by a Chi-squared test, a Chi-squared test for trend (linear by linear) or a Fishers exact test.

Finally, sensitivity of mammography and MRI were separately calculated for tumors of different sizes (≤1 cm, 1-2 cm, >2 cm), lymph node status (negative/positive), type of histology and ER status (negative/positive). For each of these characteristics, sensitivity of mammography and MRI was compared with a Mc Nemar Chi squared test. All statistical analyses were performed by SPSS version 10.1. A two-sided p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Eligibility

Within a total follow-up time of 5249 women years, 50 breast cancers were detected, of which 45 were included in the current analysis (Table 1). Reasons for the exclusion of five cancers were: the tumor was detected in women not screened according to the study protocol (n=3), because of pregnancy (n=2) or refusal of MRI (n=1); the tumor was detected by means of an additional mammography, after a screening mammography classified as BI-RADS "O", but at another location as the first lesion (n=1); the tumor was detected at a screening visit that consisted of only a clinical breast examination (n=1). The size of the excluded tumors was in one case ≤1cm, another was 15 mm, in three cases >2cm (21, 22 and 35mm). Four tumors had negative lymph nodes, one positive. One was grade 2, three were grade 3 and of one grade was unknown. Three were from ductal histotype, one lobular and one was medullary.

Table 1. Detection method of the 51 tumors.

	All detected tumours			Tumours detected in mutation carriers
	N	%	Detection rate per 1000 women years	N (detection rate per 1000 women years)
Total number of malignancies	51 (1 LY)			23
Total number of breast cancers (invasive + DCIS)	50 (6xDCIS)		9.5	23 (26.5)
Not evaluable for detection method	5 (1 interval carcinoma)			3
Evaluable	45	100	8.8	19 (21.9)
Mode of detection				
Only by MRI	22 (2x also by CBE)	49	4.2	10 (11.5)
By both MRI and mammography	10 (3x also by CBE)	22	1.9	4 (4.6)
Only by mammography	8 (2x also by CBE)	18	1.5	2 (2.3)
Only by CBE	1	2	0.2	0
Interval carcinoma	4	9	0.8	3 (3.5)

CBE denotes Clinical Breast Examination; LY malignant lymphoma.

Detection rate by detection method

Of the 45 included cancers, four (9%) were interval cancers (Table 1). Twenty-two (49%) cancers were detected by MRI and not visible at mammography of which 20 (44%) cancers were non-palpable and thus detected by MRI-only. These 20 MRI-only detected cancers were diagnosed within a total follow-up time of 5249 years (detection rate 3.8 cases per 1000 years at risk). In the subgroup of 358 mutation carriers, 10 (53%) breast cancers were detected by MRI-only in a total of 867 follow-up years (detection rate 11.5 cancers per 1000 years at risk).

Eight tumors (18%) were detected by mammography, and not visible at MRI of which six (13%) were not palpable and therefore detected by mammography only. The detection rate of non-palpable tumors by mammography only was 1.1 tumors in 1000 years at risk (six breast

cancer cases in 5249 years), and in mutation carriers 2.3 cases in 1000 years at risk (two cases in 867 years). Ten cancers were detected by both mammography and MRI (22%) of which three were also palpable. One cancer (2%) was only detected by CBE and was missed by both mammography and MRI, resulting in a detection rate for CBE only of 0.2 tumors per 1000 years at risk (one breast cancer in 5249 years).

Tumor characteristics

Characteristics of the four interval carcinomas have been described before [4]. In summary, the size of 3 interval cancers was 45, 30 and 13mm respectively, while a fourth one (4mm) was found in a prophylactic mastectomy specimen.

The only cancer detected by means of clinical breast examination, and missed by mammography and MRI, was a ductal carcinoma, with a diameter of 10 mm, Bloom and Richardson differentiation grade I, ER/PgR positive and positive lymph nodes.

In Table 2, the characteristics of MRI-only detected tumors were compared with those of all other screen-detected tumors and non-palpable, other screen-detected tumors. Eleven of the 19 invasive tumors detected by MRI-only were ≤1 cm (58%) compared with 5/16 all other screen-detected tumors (31%; p=0.11), and 2/9 non-palpable, other screen-detected tumors (22%; p=0.19). The node positivity rate was 6% in MRI-only detected tumors in comparison with 44% (p=0.02) in all other screen-detected tumors and 33% (p=0.10) in the non-palpable, other screen-detected tumors. No major differences were found with respect to differentiation grade, MAI, ER and PgR status between tumors detected by MRI-only and all other (non-palpable) screen-detected tumors.

Comparing the breast cancer characteristics of cancers detected by mammography and missed by MRI with that of cancers detected by MRI and missed by mammography, we found that DCIS was more often found at mammography (63%) than by MRI (5%; p=0.02).

Sensitivity in relation to tumor characteristics

In table 3, sensitivity of mammography and MRI is presented for different tumor characteristics. For nearly all tumor characteristics MRI was significantly more sensitive than mammography, especially with respect to smaller invasive tumors, node-negative tumors, and non-ductal carcinomas. For DCIS however, mammography appeared to be non-significantly more sensitive than MRI, although the difference was not significant.

DISCUSSION

In this analysis, we found that a large proportion of the included breast cancers was detected solely by MRI (20/45 cancers, 44%), being 40% of the total group of 50 breast cancers detected in the MRISC study. On average, 3.8 cancers per 1000 women-years were detected by MRI-only and thus missed by mammography and clinical breast examination. In the group of 358 BRCA1/2 mutation carriers, 10 out of 23 cancers were detected by MRI-only, within a total follow-up time of 867 years (11.5 cancers per 1000 women years).

Although more cancers were detected only by MRI (20 cancers, as compared to 6 cases detected only by mammography), mammography can detect tumors that are not detected by

Table 2. Tumor characteristics MRI-only detected breast cancers and all and non-palpable other screen-detected breast cancers.

	Screen-detected total		MRI detected only		Other screen-detected		Other screen-detected (not palpable)			
	N*	%	N	%	N	%	N	%	P#	P†
Total	41		20		21		13			
Tis	6	14	1	5	5	24	4	31	0.18	0.07
T≤ 1cm	16	46	11	58	5	31	2	22	0.11	0.19
T 1-2 cm	13	37	6	32	7	44	6	67		
T>2 cm	6	17	2	10	4	25	1	11		
N0	25	76	16	94	9	56	6	67	0.02	0.10
N+	8	24	1	6	7	44	3	33		
Grade I	18	51	11	58	7	44	4	44	0.52	0.40
Grade II	7	20	3	16	4	25	1	12		
Grade III	10	29	5	26	5	31	4	44		
MAI 0-5	19	58	11	61.1	8	53	4	44	0.30	0.14
MAI 6-20	7	21	5	27.8	2	13	1	12		
MAI>20	7	21	2	11.1	5	33	4	44		
ER-	11	33	7	39	4	27	3	33	0.46	1.00
ER +	22	67	11	61	11	73	6	67		
PgR-	11	33	7	39	4	27	3	33	0.46	1.00
PgR+	22	67	11	61	11	73	6	67		
Ductal	24	69	12	64	12	75	8	89	0.22	0.45
Lobular	4	11	1	5	3	9	0	0		
Tubular	4	11	4	21	0	0	0	0		
Medullary	2	6	1	5	1	6	1	11		
Adenoid cystic	1	3	1	5	0	0	0	0		

MAI denotes Mitosis Activity Index, ER denotes Estrogen Receptor, PgR denotes Progesterone Receptor.

*Total numbers can differ between various characteristics due to missing values.

#p-value between MRI detected only and other screen-detected cancers.

†p-value between MRI detected only and non-palpable other screen-detected cancers.

MRI or palpation, especially DCIS. Five of the six cases of DCIS in our analysis were detected by mammography and missed by MRI, while four of these five cases of DCIS were also not palpable. Thus, mammographic screening is therefore still needed for the detection of DCIS. This is in line with the findings from the British study,[6] but in contrast to the results regarded by Warner et al.[5] The German study did not report the method of detection of the 7 cases of DCIS, but in that study only one tumor was detected by mammography and missed by MRI (being DCIS with a micro-invasive component).[7] While a recent diagnostic study also found that MRI was more sensitive than mammography for detecting DCIS,[11] it is known that the sensitivity of MRI for the detection of DCIS is highly variable, ranging from 40%-100% in the reported studies (reviewed in refs 23-25). Further, in all screening studies, including

ours, the number of detected cases of DCIS was very small. So more data are needed on this issue in order to more accurately assess the sensitivity of MRI and mammography regarding the detection of DCIS. Also, it should be further investigated whether mammography can be performed less frequently, for instance every two years instead of yearly.
The five tumors being not evaluable for the method of detection had more unfavorable tumor characteristics than the evaluable cancers: Three of the five cancers were >2 cm in size and three were poorly differentiated. This may be due to the fact that three of these five women were not screened according to the screening protocol.

Table 3. Sensitivity of mammography and MRI for different tumor characteristics.

		Sensitivity		
	Number *	Mammography	MRI	P-value
DCIS	6	84	17	0.22
≤ 1cm	18	17	78	0.003
1-2 cm	13	54	85	0.29
> 2cm	8	38	75	0.25
N0	29	28	79	0.001
N+	8	63	75	1.00
Ductal total	26	42	77	0.04
Ductal grade 1	13	39	69	
Ductal grade 2	4	50	100	
Ductal grade 3	9	44	78	
Not ductal total	13	15	85	0.004
Lobular	4	25	100	
Tubular	4	0	100	
Medullary	4	25	50	
Adenoid cysteus	1	0	100	
ER negative	14	29	79	0.02
ER positive	23	35	83	0.007

*Total numbers can differ between various characteristics due to missing values.

In our previous study with general results of the MRISC study, we showed that intensive surveillance by the means of MRI, mammography and CBE was able to detect hereditary breast tumors in a more favorable stage as compared with age-matched symptomatic controls.[4] In the current detailed study we found that the invasive cancers detected by MRI-only were smaller and significantly more often lymph-node negative than the other screen-detected tumors. Because palpable tumors most likely were the screen-detected tumors with the largest diameter, we also compared the MRI-only detected tumors with non-palpable other screen-detected tumors. Although there were no significant differences between MRI-only detected tumors and non-palpable other screen-detected tumors regarding tumor characteristics, MRI-only detected tumors were clearly smaller and more often node-negative. These findings form additional data indicating that MRI has an important contribution to the early diagnosis of breast cancer in the MRISC study.

In a recent study it was predicted by a computer simulation model that adding a MRI to the screening program consisting of mammography and clinical breast examination would increase breast cancer mortality reduction with about 40%.[8] For mutation carriers, the addition of a MRI was cost-effective, but in other risk groups the cost-effectiveness was less favorable.

Especially for small, node-negative tumors, MRI was significantly more sensitive than mammography. For larger and node positive tumors this difference was not clear because mammographic sensitivity is already relatively high for this type of tumors. MRI was significant more sensitive than mammography for as well ductal as non-ductal cancers, but with the largest difference in sensitivity for non-ductal cancers. If the difference between sensitivity of MRI and mammography is most obvious for non-ductal cancers should be confirmed in larger series, preferentially separately for lobular, tubular and medullary cancers. We did not adjust for other variables that are correlated with sensitivity and tumor characteristics. For example, breast cancer due to a BRCA1 mutation is associated with a higher percentage of medullary tumors, a higher grade, and ER negativity at one side [26], but a lower sensitivity of mammography, not MRI, on the other side.[27] A younger age is associated with larger and more node positive tumors and with a lower sensitivity of mammography, but not of MRI.[27] This means that correction for mutation status and/or age would have increased the observed differences in sensitivity between mammography and MRI in the abovementioned groups.

In conclusion, MRI is more sensitive than mammography for a wide spectrum of tumor characteristics. Only for DCIS, mammography was (non-significantly) more sensitive than MRI. In this study additional results are provided suggesting that MRI had an important contribution to the early diagnosis of tumors in the MRISC study. These results strengthen the evidence for the recent recommendation to add MRI to the breast cancer screening program for BRCA1/2 mutation carriers. In the other risk groups, MRI should only performed in a research setting, until longer follow-up and results from larger datasets are available.

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CHAPTER 7

Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer

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Abstract

Background The MRISC study is a screening study, in which women with an increased risk of hereditary breast cancer are screened by a yearly mammography and MRI, and half-yearly clinical breast examination. The sensitivity found in this study was 40% for mammography and 71% for MRI and the specificity was 95 and 90%, respectively. In the current subsequent study we investigated whether these results are influenced by age, a BRCA1/2 mutation, menopausal status and breast density.

Patients and methods From November 1999 to October 2003, 1909 eligible women were screened and 50 breast cancers were detected. For the current analysis, data of 4134 screening rounds and 45 detected breast cancers were used. For both imaging modalities, screening parameters, receiver operating characteristic (ROC) curves and uni- and multivariate odds ratios (ORs) were calculated. All analyses were separately performed for age at entry (<40, 40-49, ≥50), mutation status, menopausal status and breast density.

Results Sensitivity of MRI was decreased in women with high breast density (adjusted OR 0.08). False-positive rates of both mammography (OR_{adj} 1.67) and MRI (OR_{adj} 1.21) were increased by high breast density, that of MRI by pre-menopausal status (OR_{adj} 1.70), young age (OR_{adj} 1.58 for women 40-49 years versus women ‡50 years) and decreased in BRCA1/2 mutation carriers (OR_{adj} 0.74). In all investigated subgroups the discriminating capacity (measured by the area under the ROC-curve) was higher for MRI than for mammography, with the largest differences for BRCA1/2 mutation carriers (0.237), for women between 40 and 49 years (0.227) and for women with a low breast density (0.237).

Conclusions This report supports the earlier recommendation hat MRI should be a standard screening method for breast cancer in BRCA1/2 mutation carriers.

INTRODUCTION

Guidelines for breast cancer screening in women with a familial or genetic predisposition mostly consist of yearly mammography and half-yearly clinical breast examination.[1] Some studies suggested that screening by mammography is insufficiently effective, especially in BRCA1/2 mutation carriers, because the sensitivity of screening is relatively low and a high incidence of interval cancers is reported in this group.[2-4] Because of this low sensitivity of mammographic screening, prospective studies were initiated in different countries to investigate the value of MRI screening compared to mammographic screening.[5-9] The main results of our national Dutch MRISC study have recently been published.[6] In this study, 50 breast cancers were detected in 1909 women within a median follow-up of 2.9 years. MRI appeared to be a more sensitive screening method than mammography (overall sensitivity 71 vs. 40%), but less specific (overall specificity 90 vs. 95%). For invasive breast cancer the difference in sensitivity between MRI and mammography was even larger: 80% versus 33%, respectively. In addition, we found that the tumor stage of the breast cancers diagnosed in the MRISC cohort was more favorable than those in an aged-matched symptomatic control group.

One of the major conditions for reaching the ultimate goal of breast cancer screening, i.e. reducing breast cancer mortality against acceptable costs and side effects, is a highly sensitive and specific screening test. Sensitivity and specificity of a breast cancer screening test are influenced by characteristics of the screened population, such as age, breast density and/or hormonal factors. From published studies the age-dependency of mammographic sensitivity is well-known, with a lower sensitivity at a young age.[10-15] persisting after adjustment for breast density.[16-18] A non-significant trend towards a lower sensitivity was found in pre-menopausal as compared to post-menopausal women, after adjustment for age and breast density.[13,19] A family history of breast cancer, and especially a BRCA1/2 mutation carriership, has been reported to be associated with a decreased sensitivity of mammography.[2,11,20,21]

Dense glandular breast tissue is associated with a decreased sensitivity of mammography,[11,12,22] also after adjustment for age.[13,16-18,23] Results with respect to the effect of hormone replacement therapy (HRT) and the sensitivity of mammography are inconsistent. Some studies found that HRT was negatively correlated with sensitivity,[24,25] even after adjustment for age[10,12,19] and breast density.[26] However, other studies failed to find an independent association of HRT with sensitivity after adjustment for age and breast density,[16,27] although HRT might still decrease sensitivity by increasing the breast density.

The effect of these factors on specificity of mammography screening has been less thoroughly investigated. These studies found that specificity is decreased by younger age, higher breast density, HRT and pre-menopausal status.[16,19,24,27]

In contrast to mammography, the effects of the factors described above on the sensitivity and specificity of MRI have never been extensively investigated in a screening setting. However, it has been reported that sensitivity of contrast-enhancing MRI in a diagnostic setting is not or only scarcely influenced by breast density.[28-30] On the other hand, hormonal factors such as

menstrual/menopausal status, HRT and also breast density have been shown to influence parenchymal contrast medium enhancement behavior of breast tissue, which might influence the sensitivity of MRI.[31] Therefore, in pre-menopausal women, MRI can best be performed in the second week of the menstrual cycle, because in this period diffuse and focal contrast enhancement of breast tissue is the lowest. Diffuse and focal contrast enhancement also occurred in at least 30% of women using HRT.[32-35] One study reported that contrast medium enhancement in women 35-50 years of age was higher than in women younger than 35 or older than 50 years.[35]

The women participating in the MRISC study vary in risk, age, menopausal status and other characteristics. In this study we investigated whether these factors influence the sensitivity and specificity of both mammography and MRI. Results might be helpful in developing more optimal screening advises for different subgroups of genetically susceptible women. Since MRI is an expensive and time consuming method compared to mammography, it is important to better define the subgroups of women for whom MRI has a high additional value and consequently offer them this type of screening.

PATIENTS AND METHODS

The MRISC study is an ongoing national multicenter screening study in women with an increased breast cancer risk due to a familial or genetic predisposition, being seen at a family cancer clinic. The study was approved by the ethics committees of all the participating centers and all participants gave written informed consent. The methods and first results of this study have been described before.[5,6] The inclusion criteria were a cumulative lifetime risk (CLTR) of breast cancer due to a genetic or familial predisposition of 15% or more, according to the modified tables of Claus,[5,36] and an age between 25 and 70 years. Women at an age younger than 25 were eligible if they had a family member diagnosed with breast cancer before 30 years, since screening could be started in that age-category at an age 5 years younger than the youngest family member was diagnosed with breast cancer. Women with symptoms suggestive for breast cancer or a personal history of breast cancer were excluded.

The surveillance scheme consisted of clinical breast examination every 6 months in addition to a 2-view mammography and a dynamic breast MRI with gadolinium containing contrast medium each year (within a 6-weeks period). The mammography and MRI were scored in a standard way according to the Breast Imaging Reporting and Data System (BI-RADS) final assessment categories, blinded from each other. The categories in this scoring system were 1 “negative” 2 “benign finding” 3 “probably benign finding” 0 “need additional imaging evaluation” 4 “suspicious abnormality” and 5 “highly suggestive for malignancy”. A screening exam was defined as positive if the BI-RADS category was 3, 0, 4 or 5, because in this case according to the study protocol additional examination was indicated. A result was called false negative if the BIRADS category of a test was 1 or 2 and if cancer was detected by either one of the other modalities or a cancer was detected within a year interval. The diagnosis of a malignant tumor was based on the results of histologic examination and all breast cancer specimens were reviewed by an expert pathologist.

Breast density was scored on mammography by the institutional radiologist, according to the BI-RADS breast composition classification:[37] BI-RADS 1 "the breast is almost entirely fat (less than 25% glandular)"; BI-RADS 2 "there are scattered fibroglandular densities (approximately 25-50% glandular)"; BI-RADS 3 "the breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51-75% glandular)" and BIRADS 4 "the breast tissue is extremely dense, this may lower the sensitivity of mammography (>75% glandular)". For this analysis, BI-RADS 1 and 2 scores were combined and called "low breast density" and BI-RADS 3 and 4 scores were called "high breast density".

At enrolment, birth date, mutation status and hormonal factors of the participating women were registered. At each follow-up visit this information was updated. In this report we used age, breast density and hormonal factors as assessed at the time of screening, whereas mutation status as assessed at the end of the study period was used.

The participants were divided into three age groups: younger than 40, between 40 and 49 and 50 years and older. For risk status we distinguished between mutation carriers (CLTR 50-80%) and non-mutation carriers (CLTR 15-50%). For menopausal status, two groups were considered: the first consisted of pre-, peri-menopausal and post-menopausal women using HRT (hereafter called 'pre-menopausal'); the second group consisted of post-menopausal women not using HRT (hereafter called "post-menopausal").

Study Population

From November 1999 until October 2003, 1952 women were included in the MRISC study. Eight women withdrew from the study before their first screening visit and another 35 were excluded because they ultimately were identified as non-mutation carriers in a BRCA1/2 family, and therefore had a CLTR < 15%.[6] In the remaining 1909 participants, 51 cancers were detected, consisting of 44 invasive breast cancers, 6x DCIS and one lymphoma in the breast, within a median follow-up time of 2.9 years. The characteristics of the study population were described before.[6] We selected all screening rounds in these 1909 women whereby both mammography and MRI were performed. Screening rounds in which one of the tests was technically inadequate or the BI-RADS final assessment category was unknown were excluded. Screening results of women with protheses in the breast were also excluded. In the current study, in total 4134 screening rounds in 1779 women were included. In this group, 45 breast cancers that were evaluable by both MRI and mammography, were detected (39 invasive cancers and six cases of DCIS). The mean age at entry of the participants was 40 years (range 19-72). The group of 1779 women consisted of 334 proven mutation carriers (19%), of whom 257 with a BRCA1 mutation, 72 with a BRCA2 mutation, one with a BRCA1 and BRCA2 mutation, two with a PTEN mutation and two with a P53 mutation.

Statistics

Sensitivity, false positive rate (1-specificity) and positive predictive value for both mammography and MRI were calculated for the different subgroups with respect to mutation status, age category, breast density score and menopausal status. Sensitivity, false positive

rate and positive predictive value (PPV) were compared between the different subgroups with the use of a Pearson's χ^2-test, a Fishers exact test or a χ^2-test for trend. The differences between sensitivity and false positive rate of mammography and MRI were tested by a Mc Nemar χ^2-test.

We used univariate and multiple logistic regression analysis to calculate the Odds Ratio (OR) for the effects of age, mutation status, breast density and menopausal status on the sensitivity (or true positive rate) and the false positive rate of mammography and MRI. In the multiple logistic regression the OR for age was adjusted for mutation status and breast density, the OR for mutation status was adjusted for menopausal status and breast density, the OR for breast density for mutation and menopausal status and the OR for menopausal status for mutation status and breast density.

For MRI and mammography we also generated receiver operating characteristics (ROC) curves for the different subgroups. The area under the curves (AUCs), which is a measure for the discriminating capacity of a test, were compared by a Z-test. A two-sided P-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of either SPSS software (version 10.1) or STATA software (version 8.2).

RESULTS

In Table 1 characteristics of women for true-positive and false-negative screening visits and also for true-negative and false-positive screening visits are presented. In total there were 45 true-positive and false-negative screening visits (screening visits ultimately followed by breast cancer within 1 year). Another 1870 screening visits had a true-negative or false-positive result.

Sensitivity

In Table 2 the sensitivities per risk, age, menopausal status, and breast density categories are presented, as well as the uni- and multivariate ORs for the effect of these factors on sensitivity. The percentages and univariate ORs showed unadjusted effects of the different factors on sensitivity. As expected, the sensitivity of mammography was decreased in case of a BRCA1/2 mutation, a lower age, a pre-menopausal status and a higher breast density, although not significantly. Sensitivity of mammography for all breast cancers (including DCIS) decreased from 46.2% in non-mutation carriers to 31.6% in mutation carriers (P=0.32) and from 55.6% in women of 50 years and older to 33.3% in women younger than 40 years (P=0.30). For pre-menopausal women sensitivity of mammography was 36.4% and this was lower than for post-menopausal women where this was 62.5% (P=0.24) and women with a high breast density had a lower sensitivity of mammography than women with a low breast density (37.9% vs. 46.7%; P=0.58). In the multivariate analyses, the same non-significant trends of a lower sensitivity of mammography were found for women with a mutation, a lower age, a pre-menopausal status or a higher breast density.

For MRI, a decreasing sensitivity in mutation carriers, younger women or pre-menopausal women are less clear than for mammography in the unadjusted analysis. Results for age and

Table 1. Characteristics of women for true-positive and false-negative screening visits and for true-negative and false positive screening visits of combined screening.

Risk	Mutation carriers								Non-mutation carriers								
Menopausal status	Pre-menopausal			Post-menopausal			Unknown		Pre-menopausal			Post-menopausal			Unknown		
Breast density	Low	High	Unknown	Low	High	Unknown	Low	High	Low	High	Unknown	Low	High	Unknown	Low	High	Unknown
True-positive and false-negative screening (n=45)																	
XM+ MRI+	1	1	-	1	0	-	-	1	4	1	-	0	1	-	-	-	-
XM+ MRI-	0	2	-	0	0	-	-	-	1	2	-	0	3	-	-	-	-
XM- MRI+	3	5	-	0	2	-	-	-	3	4	1	0	1	-	2	1	-
XM- MRI-	0	3	-	0	0	-	-	-	0	2	-	0	0	-	-	-	-
Total	4	11	-	1	2	-	-	1	8	9	1	0	5	-	2	1	-
True-negative and false-positive screenings (n=4089)																	
XM+ MRI+	3	1	-	0	0	-	1	1	5	18	-	1	1	-	-	1	-
XM+ MRI-	6	13	3	1	2	1	3	-	33	71	2	15	13	-	3	7	-
XM- MRI+	12	25	-	5	3	-	1	3	107	153	4	19	16	-	12	24	-
XM- MRI-	189	230	1	108	54	1	17	22	961	1216	22	294	192	4	74	114	1
Total	210	269	4	114	59	2	22	26	1106	1458	28	329	222	4	89	146	1

XM means mammography.

menopausal status did not clearly change after adjustment for risk categories and breast density. However, regarding breast density, the sensitivity of MRI for all cancers was 58.6% in women with a high breast density, which was significantly lower than in women with a low breast density, where this percentage was 93.3% (P=0.03). The effect remained significant (P=0.04) after adjustment for mutation status and menopausal status (OR 0.08 [95% CI 0.01-0.84]).

Table 2. Sensitivity for different subgroups and crude and adjusted odds ratios (OR) with 95% confidence interval (CI) for factors affecting sensitivity.

			Mammography				MRI			
		Cancers	Sensitivity		Univariate	Multivariate	Sensitivity		Univariate	Multivariate
		All (invasive)^ n	All# %	Invasive %	OR (95% CI)	OR (95% CI)	All# %	Invasive %	OR (95% CI)	OR (95% CI)
CLTR	15-50%	26 (23)	46.2	39.1	1	1	69.2	78.3	1	1
	50-80%	19 (16)	31.6	25.0	0.54 (0.16-1.86)	0.34 (0.09-1.37)*	73.7	81.3	1.24 (0.33-4.65)	1.98 (0.44-8.86)*
	P-value		0.32	0.36	0.33	0.13	0.75	0.82	0.75	0.37
Age	>50	9 (8)	55.6	50.0	1	1	66.7	75.0	1	1
	40-49	18 (17)	38.9	35.3	0.51 (0.10-2.57)	0.58 (0.11-3.00)†	83.3	88.2	2.50 (0.39-16.05)	2.77 (0.34-22.25)†
	<40	18 (14)	33.3	21.4	0.40 (0.08-2.06)	0.53 (0.09-3.04)†	61.1	71.4	0.79 (0.15-4.21)	0.74 (0.09-5.94)†
	P-value		0.30	0.17	0.54	0.75	0.54	0.68	0.34	0.36
Menopausal status†	Post-menopausal	8 (6)	62.5	50.0	1	1	62.5	83.3	1	1
	Pre-menopausal	33 (29)	36.4	31.0	0.34 (0.07-1.69)	0.29 (0.05-1.62)†	69.7	75.9	1.38 (0.28-6.92)	0.74 (0.13-4.37)†
	P-value		0.24	0.39	0.19	0.16	0.69	1.00	0.70	0.74
Breast density	Low	15 (14)	46.7	42.9	1	1	**93.3**	**100**	**1**	**1**
	High	29 (24)	37.9	29.2	0.70 (0.20-2.47)	0.42 (0.10-1.78)‡	**58.6**	**66.7**	**0.10 (0.01-0.88)**	**0.08 (0.01-0.84)‡**
	P-value		0.58	0.39	0.58	0.10	**0.03**	**0.02**	**0.04**	**0.04**

CLTR means cumulative lifetime risk.

Including DCIS.

*Multivariate adjusted for menopausal status and breast density.

†Multivariate adjusted for hereditary risk and breast density.

‡Multivartiate adjusted for hereditary risk and menopausal status.

^Numbers can differ due to missing values.

False positive rate

Table 3 presents false positive rates per subgroup and the univariate and multivariate ORs for the effect of these factors on false positive rate. Remarkable, we found a lower false positive rate for mammography in women younger than 40 years (3.9%) than in women aged 40-49

(6.3%) and in women older than 50 years (5.4%) (P=0.03). As expected, the false positive rate for mammography was lower in women with a low breast density compared to women with a high breast density (3.8 vs. 5.9%, respectively; P=0.002). The false positive rate of mammography was not significantly affected by mutation carriership or menopausal status. Results did not essentially change after correction for the other variables.

Table 3. False positive rate for different subgroups and crude and adjusted odds ratios (OR) with 95% confidence interval (CI) for factors affecting false positive rate.

			Mammography			MRI		
		Tests^	False positive rate	Univariate	Multivariate	False positive rate	Univariate	Multivariate
		n	%	OR (95% CI)	OR (95% CI)	%	OR (95% CI)	OR (95% CI)
CLTR	15-50%	3383	5.0	1	1	10.7	1	1
	50-80%	706	5.0	0.99 (0.68-1.43)	0.80 (0.52-1.22)*	7.8	0.71 (0.53-0.95)	0.74 (0.54-1.02)*
	P-value		0.94	0.94	0.29	0.02	0.02	0.06
Age	>50	877	5.4	1	1	7.6	1	1
	40-49	1387	6.3	1.18 (0.82-1.70)	1.10 (0.76-1.60)†	12.1	1.66 (1.23-2.24)	1.58 (1.17-2.13)†
	<40	1825	3.9	0.71 (0.49-1.04)	0.64 (0.43-0.95)†	9.9	1.33 (0.99-1.78)	1.28 (0.95-1.73)†
	P-value		0.03	0.009	0.004	0.24	0.003	0.009
Menopausal status	Post-menopausal	730	4.7	1	1	6.2	1	1
	Pre-menopausal	3075	5.0	1.09 (0.74-1.59)	0.98 (0.66-1.44)†	10.7	1.82 (1.31-2.51)	1.70 (1.23-2.36)†
	P-value		0.67	0.67	0.90	<0.001	<0.001	0.001
Breast density	Low	1870	3.8	1	1	8.9	1	1
	High	2180	5.9	1.58 (1.17-2.13)	1.67 (1.22-2.28)‡	11.3	1.31 (1.06-1.60)	1.21 (0.97-1.51)‡
	P-value		0.002	0.003	0.001	0.01	0.01	0.09

CLTR means cumulative lifetime risk.

*Multivariate adjusted for menopausal status and breast density.

†Multivariate adjusted for hereditary risk and breast density.

‡Multivartiate adjusted for hereditary risk and menopausal status.

^Numbers can differ due to missing values.

Interestingly, the false positive rate of MRI was lower in BRCA1/2 mutation carriers than in non-mutation carriers (7.8 vs. 10.7%; P=0.02). Further, the false positive rate of MRI was higher in pre-menopausal than in post-menopausal women (10.7 vs. 6.2%; P < 0.001), and in women with a high breast density versus low breast density (11.3 vs. 8.9%; P=0.01). Additionally, the false positive rate was higher in women younger than 50 years than in older women. Using univariate ORs this finding was significant for women 40-49 years (OR 1.66

[95% CI 1.23-2.24], but not for women younger than 40 years (OR 1.33 [95% CI 0.99-1.78 Results did not alter after adjustment for other factors.

PPV

In Table 4, PPV for the different subgroups are presented. The number of positive tests was higher for MRI than for mammography, because MRI more often had false-positive and true-positive test results than mammography. As the PPV depends on the incidence rate, it is expected to be higher in subgroups with a higher breast cancer incidence. There was indeed a trend that the PPV of mammography was higher in mutation carriers (14.6%) than in non-mutation carriers (6.6%; P=0.08). Further, the PPV of mammography was not clearly different between subgroups according to age, menopausal status and mammographic breast density.

Table 4. Positive predictive value* for different subgroups.

		Mammmography		MRI	
		Number of positive tests†	%	Number of positive tests†	%
CLTR	15-50%	182	6.6	379	4.7
	50-80%	41	14.6	69	20.3
	P-value		0.08		<0.001
Age	<40	52	9.6	73	8.2
	40-49	94	7.4	183	8.2
	≥ 50	77	7.8	192	5.7
	P-value		0.89		0.60
Menopausal status	Post-menopausal	39	12.8	50	10.0
	Pre-menopausal	167	7.2	351	6.6
	PPvalue		0.33		0.37
Mammographic breast density	Low	78	9.0	180	7.8
	High	139	7.9	263	6.5
	P-value		0.79		0.59

CLTR means cumulative lifetime risk.

*Positive predictive value is percentage of positive tests which is true-positive.

†Numbers of tests with a BI-RAD score of 3 or higher.

Regarding MRI, the PPV was higher in mutation carriers (20.3%) than in women without a proven mutation (4.7%; P < 0.001). No clear effects of age, menopausal status and breast density on the PPV of MRI were observed.

Discriminating capacity

Sensitivity and false positive rate (1-specificity) were combined into ROC curves. The data on AUCs in the ROC curves of mammography and MRI for different subgroups are shown in Table 5. The ROC curves per risk and breast density category are presented in Figures 1, 2, respectively.

For all subgroups the AUC in the ROC curve for MRI was higher than for mammography, meaning that MRI can better discriminate between women with and without cancer. For post-

menopausal women, no clear difference was found between the AUCs for MRI and mammography. The largest differences between AUCs of MRI and mammography, in favor of MRI, were found in BRCA1/2 mutation carries (0.237; P=0.006), in women aged 40-49 years (0.227; P=0.02) and in the group with a low breast density (0.237; P=0.008).

Table 5. Area under the curve in the ROC curve of mammography and MRI for different subgroups.

		Area under the curve			
		Mammography	MRI	Difference	P-value
	Total	0.686	0.827	0.141	0.03
CLTR	50-80%	0.628	0.865	0.237	0.006
	15-50%	0.733	0.804	0.071	0.44
	P-value	0.19	0.42		
Age	<40	0.697	0.765	0.068	0.53
	40-49	0.651	0.878	0.227	0.02
	≥ 50	0.737	0.851	0.114	0.47
	P-value	0.75	0.42		
Menopausal status	Pre-menopausal	0.678	0.820	0.142	0.06
	Post-menopausal	0.776	0.778	0.002	0.99
	P-value	0.39	0.72		
Mammographic breast density	High	0.682	0.759	0.077	0.39
	Low	0.706	0.943	0.237	0.008
	P-value	0.79	0.006		

CLTR means cumulative lifetime risk.

DISCUSSION

This study investigated which factors are affecting the sensitivity and false positive rate of mammography and MRI screening in women with a familial or genetic breast cancer susceptibility. We further explored in which subgroups the MRI is mostly superior to mammography.

With respect to sensitivity, the most obvious finding of our study was that a higher breast density, adjusted for risk and menopausal status, was associated with a significantly lower sensitivity of MRI, and a lower sensitivity of mammography, although not significantly. The lower sensitivity of mammography in case of high dense breast tissue is well-known,[13,23] while no major effects of breast density were found on the sensitivity of MRI in women without a hereditary increased risk,[28-30] although it has been reported that contrast enhancement is often higher in women with dense breasts.[31] In view of these findings, the role of contrast enhancement of MRI in women with high and low breast density in relation to sensitivity should be further investigated.

Nevertheless, although the sensitivity of MRI as compared to mammography is most pronounced in women with low breast density (93.3 vs. 46.7%; P=0.04), also in women with

high breast density the sensitivity of MRI remains higher than that of mammography (58.6 vs. 37.9%; P=0.3). This is especially the case in invasive cancers (66.7 vs. 29.2%; P=0.04).
It is possible that our findings with respect to breast density in relation to the sensitivity of MRI can be partly explained by the logistic failure to perform the MRI in the most optimal phase of the menstrual cycle (between day 5 and 15 of the menstrual cycle).[5] However, also in the case that MRI was performed in the optimal phase we observed a non-significantly higher sensitivity in women with a low breast density than in women with a high breast density (80 vs. 54%, respectively) (data not shown).
In 192 of the 1776 evaluable participants (10.8%), breast density was differently scored between screening rounds with changes from high to low breast density or vice versa (data not shown). It is unknown whether this was a real change in breast density or a variation in observation. In our study, breast density was scored by different radiologists at different centers, so that inter- and intra- observer variation may play a role. Berg et al.[38] found substantial inter- and intra-observer variability in mammographic interpretation, including breast density, while other studies reported that breast density assessed by different radiologists or by a radiologist and digital assessment was well correlated.[39-41] However, it is likely that this variation was random (and not systematic), leading to a dilution of the effect. Therefore intra-observer variability is not likely an explanation for the high sensitivity of MRI in women with low breast density.
Breast density and sensitivity of mammography were not independently assessed. It might be that when a tumor is clearly present, the radiologist is more prone to score breast density as BI-RADS 1 or BI-RADS 2, combined in the “low density” group in this study. This might be result in an overestimation of the relation between a lower breast density and a higher sensitivity on mammography. However, this cannot explain the observed relation between breast density and the sensitivity of MRI in this study: as MRI and mammography were independently assessed, breast density and sensitivity of MRI were scored independently.
Contrary to breast density, the other investigated variables were not significantly affecting the sensitivity of both mammography and MRI. However, we found a trend, although not significant, of a lower sensitivity of mammography in BRCA1/2 mutation carriers, persisting after correction for breast density and menopausal status. The finding of a lower mammographic sensitivity in BRCA1/2 mutation carriers is in line with the findings in other studies.[2,3] An explanation might be the specific imaging features of BRCA1/2 mutation carriers, such as a higher frequency of prominent pushing margins resulting in solid masses more difficult to differentiate from fibroglandular tissue than more classical appearances of breast cancer.[20,42] In our study, however, the sensitivity of MRI was not lower in BRCA1/2 mutation carriers. These findings are in line with results of the British study where also a lower sensitivity of mammography and not of MRI was found in BRCA1 mutation carriers compared to non-mutation carriers.[8] In our study, we made no distinction between BRCA1 and BRCA2 mutation carriers because of the small number of detected breast cancers. The contrast between mutation carriers and non-mutation carriers may be diminished, as only 4 (15.4%) of the 26 breast cancer patients without a BRCA1/2 mutation were individuals from a proven non- BRCA1/2 family. In the families of the other 22 women DNA diagnosis was not

performed, not finished or it was unknown if DNA diagnosis was performed (data not shown). This last group may contain some unidentified BRCA1/2 mutation carriers.

In the current study we found trends, although not significant, that the sensitivity of mammography was lower in younger and pre-menopausal women. These findings are in line with other studies.[11,16,18] The most likely reason, after correction for breast density, is a higher tumor growth rate at a younger age.[43,44] On the other hand this trend was not found for MRI. However, the confidence intervals are wide thus it might be that the sensitivity of MRI is also influenced by age. Another reason might be that MRI can pick up smaller tumors and therefore its sensitivity is less influenced by tumor growth than that of mammography.

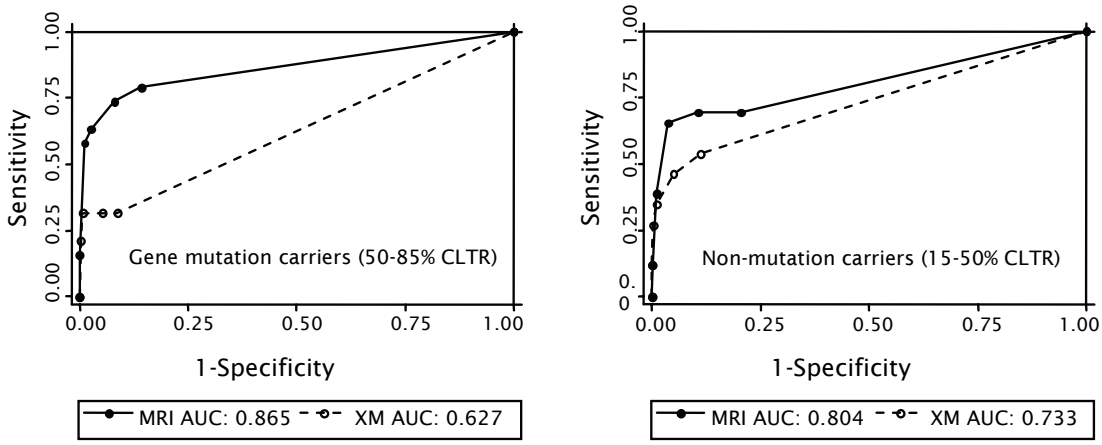

Figure 1. ROC curves for MRI and mammography for the different risk groups.

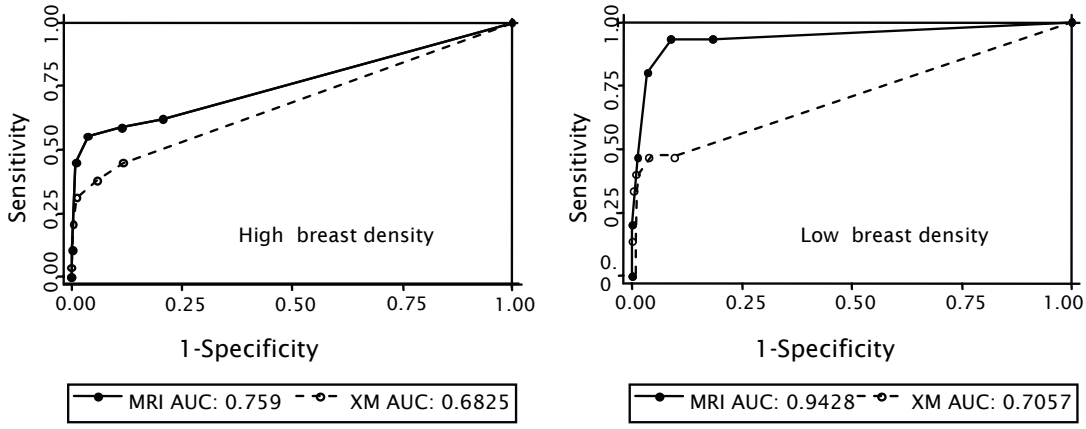

Figure 2. ROC curves for MRI and mammography for women with high and low breast density.

The precision of sensitivity estimates in our study was hampered by the small number of detected breast cancers (n=45), resulting in wide confidence intervals around the various estimates of sensitivity.

It is known that the sensitivity of mammography and MRI can differ with respect to the detection of invasive cancers and cases of DCIS,[6] and between first and subsequent screening

rounds.[45,46] In view of the small number of detected breast cancers it was not possible to perform separate analyses with respect to these factors.

A high breast density, adjusted for menopausal status and risk category, was associated with an increased false positive rate of mammography. The same result was found in the study of Carney et al..[16] High breast density also increased the false positive rate of MRI by univariate analysis, but this finding was just not significant anymore when adjusted for mutation status and menopausal status.

Our finding of a lower false positive rate of mammography in women younger than 40 years, compared to older women, was unexpected and is in contrast with the results of Carney et al.[16] who found a higher false positive rate in younger women than in older women. This higher false positive rate for younger women (< 50 years) was found for MRI in our study, also when adjusted for mutation status and breast density. Furthermore pre-menopausal women had, when adjusted for mutation status and breast density, a significantly higher false positive rate of MRI than post-menopausal women.

Strikingly, in the univariate analysis a significantly lower false positive rate of MRI was found in mutation carriers than in non-mutation carriers. Adjusted for menopausal status and breast density this finding was just not significant anymore. Although this finding was not expected, it is possible that a different pattern of benign lesions compared with non-mutation carriers might play a role in this finding.[47]

Results for the effect of breast density and mutation status on sensitivity and false positive rate were, among other factors, adjusted for menopausal status. When we adjusted for age instead of menopausal status results did not appreciably alter.

This paper is based on 4134 screening rounds of 1779 women, meaning that many women had more than one screening round and thus results of different screening rounds are not independent. This has no influence on the estimated effect, but p-values might be overestimated.

Sensitivity and false positive rate were combined in ROC curves. The area under the curve (AUC) is a measure for the discriminating capacity of a test. Subgroups in which the difference between MRI and mammography in the area under the curve is the highest have probably the most advantage of MRI-screening. Within the different risk groups, mutation carriers had the highest additional value of MRI, with a difference in AUC between MRI and mammography of 0.237 (P=0.006), compared to 0.077 in the non-mutation carriers. Reasons for the larger difference were both a lower sensitivity of mammography and lower false positive rate of MRI in BRCA1/2 mutation carriers. Also in women aged 40-49 the difference in AUC (0.227) was relatively large as compared with younger and older women. Remarkable is the great difference between the area under the curve in favor of MRI in women with low, but not in women with high breast density (AUC 0.237 and 0.077, respectively). An important reason is the larger difference in sensitivity of MRI and mammography in favor of MRI in women with a low breast density (93.3 vs. 46.7%) compared with women with a high breast density (58.6 vs. 37.9%).

In conclusion, in this study the discriminating capacity of MRI as compared to mammography was especially superior in BRCA1/2 mutation carriers, in women with a low breast density

and in women aged 40-49 years. Further, in all other investigated subgroups MRI was superior to mammography. The hypothesis that MRI has the highest additional value in women with high as compared to low breast density was not confirmed. This unexpected finding should be confirmed in larger datasets and for other cut-off levels for "high" and "low" breast density. The relatively low sensitivity of mammography as compared to MRI in BRCA1/2 mutation carriers supports the recent recommendations for the incorporation of MRI-screening in this group.

Obviously, the decision whether MRI-screening should be performed and in which subgroups, is not only based on the performance of the above mentioned screening parameters, but also on the incidence and stage of detected breast cancers, costs of screening, and ultimately on the reduction of breast cancer mortality. Larger datasets, preferentially by the pooling of the various ongoing MRI screening studies and/or longer follow-up are needed to develop more specific screening guidelines for the different subgroups of genetically susceptible women.

Acknowledgement

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CHAPTER 8

Hereditary breast cancer growth rates and its impact on screening policy

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Abstract

Imaging is often performed yearly for the surveillance of BRCA1/2 mutation carriers and women at high familial breast cancer risk. Growth of cancers in carriers may be faster as these tumors are predominantly high grade. Quantitative data on tumor growth rates in these 2 groups are lacking. Here, we have examined 80 high-risk women under surveillance for tumor size at diagnosis and preceding examinations at mammography and/or MRI. Tumor volume doubling time (DT) was assessed in 30 cancers in BRCA1/2 mutation carriers and 25 non-carriers. Impact of age and menopausal status were also evaluated. Mean DT of all invasive cancers was shorter in carriers (45 days CI: 26-73) than non-carriers (84 days CI: 58-131) (P = 0.048). Mean age at diagnosis was lower in carriers (40 years) than non-carriers (45 years) (P = 0.007). At multivariable analysis only age (P = 0.03), not risk-group (P = 0.26) nor menopause (P = 0.58) correlated significantly with DT. The mean growth rate slowed down to half in each successive 10 years-older group. In conclusion, age at detection indicated the growth rates of hereditary and familial breast cancers. It is recommended that the screening frequency should be adjusted according to a woman's age and a high-sensitive biannual test may be appropriate before the age of 40 years.

INTRODUCTION

Early detection is one of the limited options to possibly reduce the risk of mortality from breast cancer for women with a gene mutation (e.g., BRCA1, BRCA2, p53) or with a family history, indicative of an increased risk for breast cancer at a relatively young age. For BRCA1 mutation carriers, the risk of developing breast cancer before 50 years of age is as high as 50% while for BRCA2 the risk is slightly less.[1,2] Although breast cancer cells may disseminate early during tumor development,[3] tumor size and lymph node status remain strong prognostic factors for survival in breast cancer.[4-7] Screening women at hereditary risk with magnetic resonance imaging (MRI) can detect tumors at an early stage.[8,9] In the Dutch MRISC study, 78% of the detected tumors were ductal carcinoma in situ (DCIS) or smaller than 2 cm, 79% node-negative.[8] However, a higher percentage of interval cancers have been observed in BRCA1/2 mutation carriers compared with women with high familial risk without a proven mutation (non-carriers) under the same surveillance scheme.[8,10] One of the likely causes is different growth rates of tumors, as high mitotic count and high grade tumors (63% and 69%, respectively) were more frequently found in cancers from BRCA1 mutation carriers in comparison to sporadic cancers (32% and 38%, respectively) and BRCA1/2-negative hereditary breast cancers (17% and 23%, respectively).[11,12]

To our knowledge no quantitative data have been published on tumor growth rates in these hereditary risk groups based on measurements from imaging. Finding the optimal frequency at which a screening method should be applied can be as important to improve its effectiveness as the ability to detect cancers at an early stage.[13] Screening too frequently increases the medicalisation of healthy women, the risk of false-positive results, cost and radiation risk.[14] However, too low a frequency may result in a delay in diagnosing breast cancer, missing the chance to improve prognosis. In this study, we have investigated the influence of a BRCA1/2 mutation, age and menopausal status/bilateral preventive salpingo-oophorectomy (BPSO) on tumor growth rate in women at high familial risk. Based on our results, we have tried to define the optimal screening frequency for women in different risk categories.

MATERIAL AND METHODS

We could evaluate the size of 55 tumors at diagnosis and with the same radiologique technique, either mammography (Mx) or MRI, at previous screening(s), for 80 breast cancer patients examined. All tumors were detected in women under surveillance, because of: (a) a proven BRCA1 or BRCA2 mutation (carrier group), or (b) an estimated hereditary risk of 20-50% according to modified tables of Claus,[8,15] while no BRCA1 or 2 mutation could be demonstrated or no DNA investigation had been performed (non-carriers). The methods for BRCA1/2 mutation analyses are described elsewhere.[16,17]

From November 1, 1999 to July 1, 2003, 47 breast cancers were detected in women participating in the Dutch surveillance study MRISC in 2 cancer centers and 4 university hospitals. Screening consisted of clinical breast examination every 6 months and annual Mx

and MRI. Imaging technique and protocol have been previously described.[8] Tumor growth rate were evaluable in 32 cases. Thirty-three consecutive cancers were detected in the women under surveillance for the same indication outside this study after January 1, 1995 at the ErasmusMC. Surveillance for them was performed with biannual clinical examination and annual mammography. Additional MRI was performed with the same Tesla strength, intravascular contrast and subtractions as in the MRISC in 13 patients. Tumor growth rate was evaluable in 23 cases. In total, growth rates were assessed in 55 patients. In 25 patients, tumor growth rates could not be calculated as the tumor was neither measurable at diagnostic Mx or at MRI.
The diameter at pathology, mitotic count and Bloom- Richardson grading of the tumors; menopausal status and BPSO were taken from medical files.

Measurements and calculation of tumor growth rate

To estimate the growth rates of tumors, all diagnostic mammograms and MRI, were reevaluated by a radiologist (CB or IO). For all the cancers visible at the diagnostic Mx/MRI, the previous examination(s) were also reassessed. If the tumor could be clearly identified at the diagnostic MRI, 3D measurements at right angles, including the single largest dimension (SLD), were taken from the diagnostic and previous MRI. For all cancers positively identified at the diagnostic Mx, tumor size was measured at both oblique and craniocaudal views at diagnostic and previous Mx. The tumor diameter was measured using the longest axis (a = SLD) and a second maximum diameter was measured perpendicular to the first (b). For tumors measurable at both views, the largest, smallest and mean of the 2 sizes were used to calculate tumor volume. In the case of a stellate mass, the center was measured. For cancers with a measurable tumor at 2 or more subsequent mammograms or MRI and where a previous mammogram/MRI showed no visible tumor (9 Mx, 2 MRI), only the measurable tumor sizes were used for the calculation of individual tumor volume doubling time (DT). To calculate the DT of each cancer, the method (Mx or MRI) with the most measurement points was used. In case of equal number of measurements, the method with the single largest tumor diameter at diagnosis closest to the size at pathology was used. The volume of the tumor was estimated using the formula for obloid spheroids

$$V=4/3\pi \cdot 1/2a \cdot 1/2b \cdot 1/2c.$$

Tumor volumes were assumed to have exponential growth (i.e., growth with a constant volume doubling time). For patients with 2 real volume measurements, the slope of the straight line connecting the 2 log-transformed data points was calculated. In case of 3 or more real volume measurements, this slope was calculated using least-squares regression. For patients with one last real measurement and one previous undetected tumor, the latter tumor size was set at 0.004 cm^3 corresponding to a diameter of 2 mm (assumed lower detection limit). The resulting slopes for these patients therefore may under estimate the true slope.

However, not including these for the estimation of growth rates would probably exclude many of the fast growing tumors.[18] Subsequently, tumor volume doubling times were calculated using the following formula:

$DT = log2/\beta$

where β was the slope of the regression line of the logarithm of the tumor volume vs. time. This outcome may over estimate the true doubling time for patients with an undetectable tumor at the previous visit and is treated as a left-censored observation in the statistical analysis.[18]

Statistical methods

Differences in patient and tumor characteristics between the 2 risk groups were tested with the use of the t test in case of continuous variables and of the χ^2 test or Fisher's exact test in case of categorical variables. To determine the correlation between tumor size at mammography/MRI and at histopathological examination, we calculated Pearson's correlation coefficient separately for invasive cancers and ductal carcinoma in situ (DCIS). To get an approximate normal distribution of volume doubling times, these times were logarithmically transformed for analysis. Comparison of the transformed DT between risk groups was done using the t test. Multiple regression was used to evaluate simultaneously the effects of age, risk group and menopausal status. STATA software (procedure CNREG) was used in these calculations to allow for the presence of left-censored volume doubling times. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Patients and tumor characteristics

Of the total group of 55 tumors, in which growth rate could be assessed, 30 (5 DCIS, 4 of the DCIS in BRCA1) were detected in mutation carriers (25 BRCA1 and 5 BRCA2) and 25 (3 DCIS) in non-carrier women with an estimated life time risk of 20-50%. Eighteen patients in the non-carrier group had tested negative for BRCA/2, while no DNA test results were available for 7 patients. Only 1/7 tumors in the non-tested group had characteristics suggestive of a BRCA1-associated tumor (both high grade and ER and PR negative), but with a mitotic count of 3. Patient and tumor characteristics of the carrier and non-carrier groups are shown in Table 1. Mean age at diagnosis was significantly lower in carriers than in non-carriers (40 years vs. 45 years, respectively, P = 0.007); (39 years for BRCA2 and 47 years for the non-tested). Seven of the carriers were post-menopausal at diagnosis, 6 after BPSO (no BRCA2), while 6 non-carriers were naturally post-menopausal (3 non-tested). Age of post-menopausal carriers vs. non-carriers was 47.0 vs. 52.2 years, P = 0.11. Only in BRCA1 carriers, cancers were detected between follow-up visits (n = 5). Median diameters of the invasive tumors at pathology were with 12 vs. 11 mm comparable between the 2 groups

(mean = 9 (6-15) mm in 4 BRCA2). Mean mitotic count was higher in carriers than non-carriers (40 vs. 8.5, P = 0.001); (23 in BRCA2 and 7.8 in the 7 non-tested range 1-19).

Table 1. Patient and tumor characteristics in BRCA1/2 mutation carriers and non-carriers.

	BRCA1/2 carriers (n=30)	Non-carriers (n=25)	P-value
Patient characteristic			
Mean age at detection[a] (range)			
Overall	40.1 (27-52)	45.4 (31-59)	0.007
Detected pre-menopausal	38.0 (27-50)	43.1 (31-53)	0.009
Detected post-menopausal	47.0 (37-52)	52.2 (45-59)	0.11
Menopausal status[b]			
Pre-	23 (77%)	19 (76%)	0.95[c]
Post- after BPSO[d]	6 (20%)	0	0.03
Post- natural	1 (3%)	6 (24%)	
Mode of detection[e]			
Interval cancer	5 (17%)	0	0.06
Screen detected	25 (83%)	25 (100%)	
Tumor characteristics			
DCIS [f]	5 (17%)	3 (12%)	0.72
Invasive	25 (83%)	22 (88%)	
Median diameter at Pathology mm[g] (range)	12 (3-40)	11 (6-40)	
Mean mitotic count[h]	40 (1-319)	8.5 (1-43)	0.07
Bloom-Richardson grade [i]			
1	0 (0%)	5 (23%)	0.01
2	8 (36%)	10 (45%)	
3	14 (64%)	7 (32%)	

a Data were available for 30 carriers and 24 non-carriers.
b Menopausal status: number (percentage).
c Pre- vs. post-menopausal.
d BPSO (bilateral prophylactic salpingo-oophorectomy) vs. no BPSO.
e Mode of detection: number (percentage).
f DCIS ductal carcinoma *in situ.*
g Data was available for 30 carriers and 22 non-carriers (missing in 1 invasive and 2 DCIS).
h Data was available for 21invasive tumors in carriers and 16 invasive tumors in non-carriers. Number of mitosis per 2 mm^2 (range) in invasive cancers.
i Data available for invasive tumors of 22 carriers and 22 non-carriers.

Tumors were more often high grade in carriers vs. noncarriers (P = 0.01); (2 grade 3 and 2 grade 2 in BRCA2). The size of DCIS at pathology in carriers was 6-33 mm at age 32-44 years and in non-carriers 12 mm-'large' at age 31-48 years. Growth rates, for reasons mentioned in the methods section, could not be assessed in 10 carriers (2 BRCA2) with mean age 38 years (range 29-57) and 15 non-carriers (8 DNA tested) mean age 45.3 years (33-55). There were no interval cancers in this group. One tumor in these carriers was DCIS, mean

diameter of the others at pathology was 11.2 mm (2-28) and mean mitotic count was 50 (15-116). The non-carrier tumors that were not evaluable for growth rates had a mean diameter of 15.4 mm (4-45) mean mitotic count 9 (1-45).

Tumor measurements

Calculations were performed using the measurements at Mx for 34 tumors and MRI for 21. The mean time between 2 measurements was 0.9 years (range 0.3-1.8) for the total group and carriers, while for non-carriers it was also 0.9 years but with a different range from 0.4 to 1.3. Figure 1 and Table 2 gives the number of the used measurements, method and characteristics of the images (i.e., as nucleus shadow or calcifications) of the tumors in the 2 risk groups. The size of the invasive cancers at pathology correlated significantly with the estimated size at diagnostic MRI and Mx, with a correlation coefficient of 0.84 and 0.67, respectively. DCIS at pathology correlated significantly with measurements at Mx (n = 4) with a correlation coefficient of 0.99.

Table 2. Characteristics, number and modality of the measurements of the tumors in carriers and non-carriers.

Risk group	Carriers (*n*=30)	Non-carriers (*n*=25)	Total (*n*=55)
Rad. Caracteristic[a]			
Calcifications	3(3)	4(1)	7(4)
Nucleus shadow	27(2)	21(2)	48(4) 55(8)
Number of measurements			
Mx[b] ≥ 2[c]	9(2)	12(1)	21(3)
MRI ≥ 2	7	6(1)	13(1)
Mx 1 + n.o.t.[d]	7(2)	6	13(2)
MRI 1 + n.o.t.	7(1)	1(1)	8(2)
Total	30(5)	25(3)	55(8)

Between brackets number *in situ* cancers.

a Rad.: radiological.

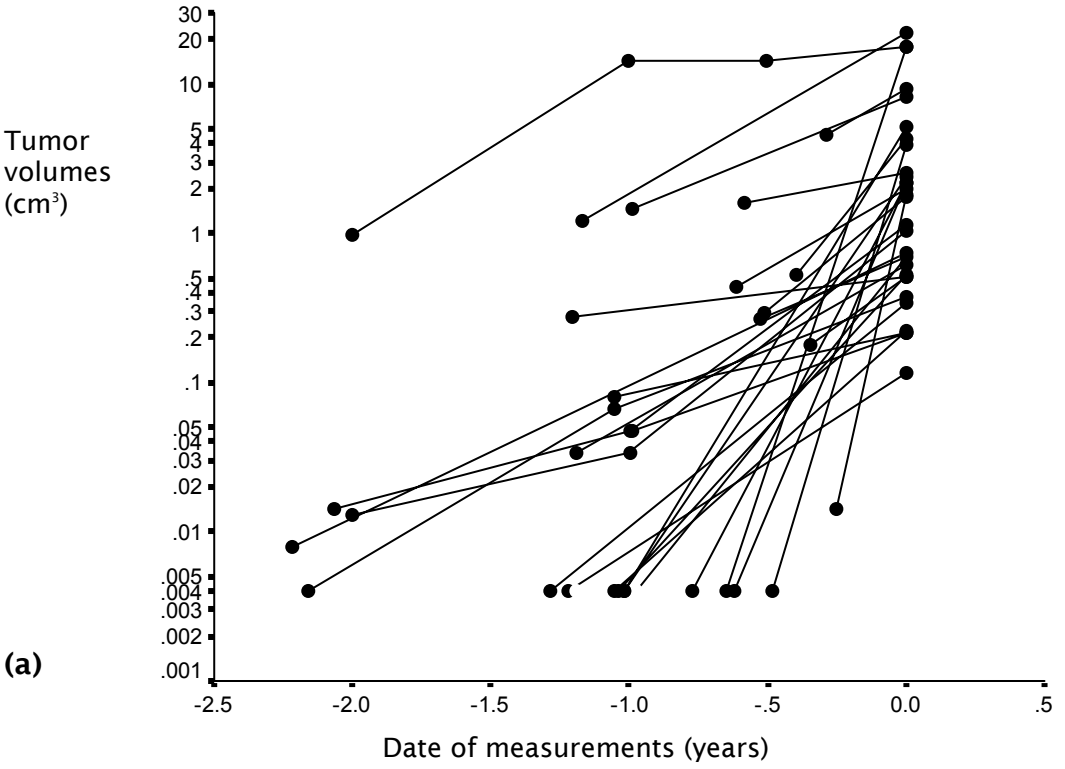
b Mx: mammogram.

c ≥ 2: measurable tumor on at least 2 consecutive images.

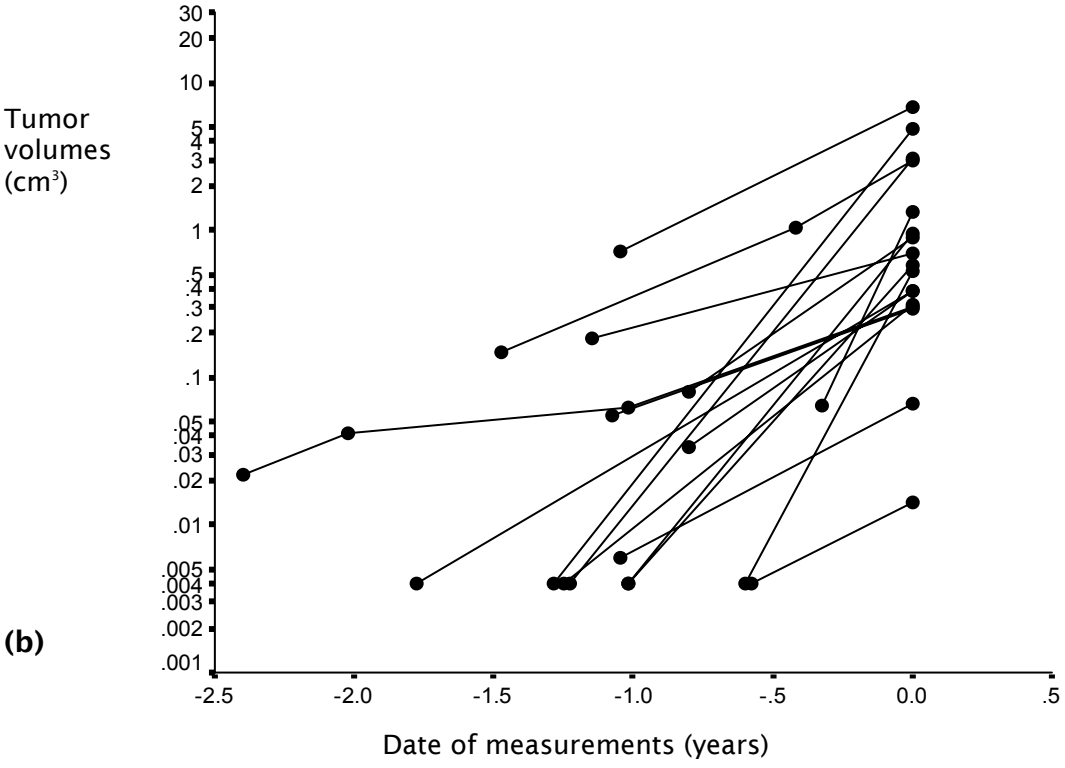
d n.o.t.: on previous imaging "no observable tumor".

Growth rate of invasive cancers in BRCA1/2 mutation carriers vs. non-carriers

Figure 2 shows the tumor volume doubling times of the invasive and in situ cancers in the 2 risk groups according to menopausal status. The geometric mean volume doubling times of the 47 invasive carcinomas and 8 DCIS were 60 and 59 days, respectively. Further analysis was restricted to the invasive tumors only. The geometric mean doubling time for carriers and non-carriers was 45 and 84 days, respectively (P = 0.048). It was further found that the doubling time increased with advancing age at diagnosis: 9.8% per year for carriers (P = 0.01) and 5.4% per year for non-carriers (P = 0.064) and these increases did not significantly differ from each other. When adjusted for the significant age difference between carriers and non-



(a)



(b)

Figure 1. Measurements at Mx (a) and MRI (b) used for the calculations of doubling times. Data points with volume = 0.004 cm^3 denote tumors undetectable at the mammograms or MRI prior to the diagnostic ones. 0.0 is time of diagnosis.

carriers (Table 1), there was no significant difference in geometric mean tumor volume doubling times between the 2 risk-groups (Table 3). Although there was a significant difference between the total group of pre- vs. post-menopausal women regarding geometric mean doubling times, 49 days vs. 115 days (P = 0.023), respectively, (this difference was 35 vs. 87 days in carriers and 75 vs. 153 days in non-carriers) significance was lost in a similar way after adjustment for age. Table 3 shows results of the multivariable analysis of logarithmically transformed tumor volume doubling times, taking into account carriership, age at diagnosis and menopausal status of the women. Only age was significantly associated with the mean doubling times. The mean of the DT was more than twice higher after a decade.

Table 3. Multivariate impact of carriership, menopausal status and age at detection on tumor Doubling Times (DT).

Factor	Multivariate ratio of geo- metric mean doubling time	95% CI	P-value at multivariate analysis
Carrier status[a]	0.7[a]	0.4-1.3	0.26
Menopausal status[b]	1.3[b]	0.6-2.8	0.58
Age[c]	1.9[c]	1.1-3.4	0.03

a Carriers vs. non-carriers.
b Post-menopausal vs. pre-menopausal.
c Per 10 years older age.

Taking account of age only, the relationship for mean values was log2 (doubling time [years]) = -7.75 + 0.12 age (standard error for the age-coefficient: 0.03, with P < 0.001). The resulting relationship is shown in Figure 3 and the associated increase of the geometric mean volume doubling time is 9% (95% CI: 4-14%) for each 1-year increase of age. This relationship did not really differ (P = 0.45) between MRI and Mx assessed doubling times (Figure 1). Nor did the multivariate analyses change substantially after exclusion of the 7 cases not tested for BRCA1 and BRCA2 (P value for risk-group 0.21, menopausal status 0.7, age 0.03). The tumor characteristics grade and mitotic count differed between the 2 risk groups. At univariate analysis, mitotic count correlated with DT (P = 0.03) while grade did not (P = 0.3). When mitotic count and grade were entered into the multivariable model the results remained essentially unchanged with P value for age, grade and mitotic count P = 0.015, P = 0.8 and P = 0.4, respectively.

DCIS

Four in situ cancers were only visible at diagnosis not on previous imaging: 3 in carriers (6, 7 and 33 mm) and 1 non-carrier (>40 mm) (Figure 2).

DISCUSSION

The growth rates of hereditary breast cancer are important to estimate the optimal test frequency for screening, be it by breast imaging (Mx or MRI) or new emerging screening tools, e.g., serum-proteomicpattern markers.[9,13,19]

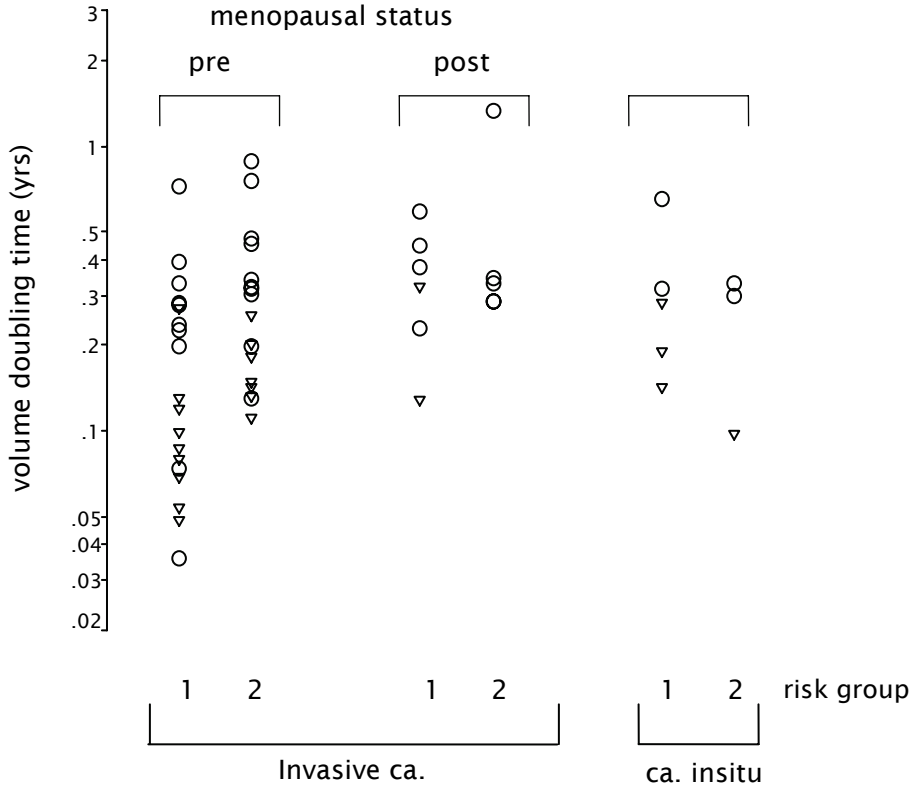


Figure 2. Tumor volume doubling times (DT) of invasive and in situ cancers according to risk group and menopausal status. 1, DT of cancers in BRCA1/2 mutation carriers; 2, DT of cancers in women at non-BRCA1/2 hereditary risk. O, calculated with ≥ 2 measurements; Δ, left censored.

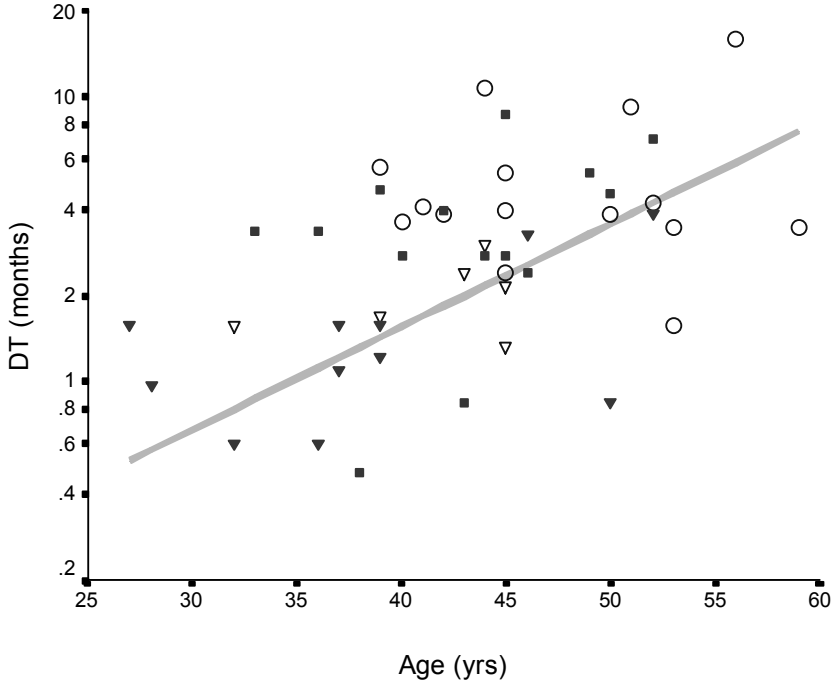


Figure 3. Tumor doubling time (DT) in months according to age at diagnosis. Solid symbols, BRCA1/2-carrier; open symbols, non-carrier. Triangles represent left-censored DTs. The increase in geometric mean volume doubling time equals 9% (95% CI: 4-14%) for each 1-year increase of age. $\log_2$(doubling time[years])=-7.75+0.12 age.

Tumor volume doubling time was 45 vs. 84 days, twice as short in invasive cancers of BRCA1/2 mutation carriers compared to non-carriers and twice as short in pre- vs. post-menopausal women. However, mean age at detection differed significantly between the 2 risk groups and carriers were more often post-menopausal at a relatively young age after BPSO. Age at diagnosis and not risk-group or menopausal status, was the only significant indicator of tumor growth rate from multivariate analysis. The on average higher tumor growth rates in carriers vs. non-carriers and pre- vs. post-menopausal women contributed apparently to earlier ages at detection. Tumors were more often high grade and the average mitotic count was higher in our younger carrier group as expected. When these indicators of growth rate were entered into the multivariate model, still only age correlated independently with the estimated tumor doubling times (P = 0.015). Tumor growth rates gradually slowed down (9% yearly) with increasing age at diagnosis, without a clear cut-off between the risk groups or at menopause.

Our study was performed in women with a well-defined hereditary risk, within surveillance schemes with complete follow-up. The relatively low number of interval cancers (in 5 BRCA1 carriers only) may be due to the rather short screening intervals. We assessed the growth rates in only 4 invasive breast cancers in BRCA2 mutation carriers, who did not differ significantly with regard to age, tumor size, grade or mitotic count from the BRCA1 mutation carriers. The DT pattern for BRCA1 mutation carriers and non-carriers of the same age were similar.

In 7 patients, no test for deleterious BRCA1/2 mutations was performed or completed. But after exclusion of those 7 cases, results from the analyses were essentially the same. In the 2 risk groups, patient and tumor characteristics did not differ between those with and without DT assessment. Therefore, DT measurements in both risk groups may be representative for that group. Measurements at Mx or MRI were used for DT calculations and both methods correlated well with size at pathology. Neither the mean doubling time nor the results at multivariable analyses differed significantly between assessments with either method.

The radiologist knew from the diagnostic imaging, where and how the cancer was depicted, therefore we estimated tumor size at the previous image with ‘‘no observable tumor’’ on retrospect, to have a max size of 2 mm. This seemed realistic as 5 tumors with MRI and 8 Mx cases were <4 mm despite high breast density. By extrapolating growth curves of tumors measurable at P2 Mx/MRI but where tumor was not detected at the previous image (9 Mx, 2 MRI), occult-tumor-size was at Mx twice <2 mm and 7 times <4 mm and at MRI twice <2 mm. Importantly, when we calculated DTs with the assumption that occult-tumor-size at Mx was <4 mm), results of the multivariable analysis did not change.

Growth may not be continuous and possibly speed up or slow down under influence of host factors or size. However, we performed calculations on the assumption that tumors will follow exponential growth, as this is usually assumed to be the best approximation for the range of tumor sizes in our study (3-40 mm).[20,21] Our findings in 12 of the 15 cases with more than 2 measurements were consistent with exponential growth, while in 1 there seemed to be a period without growth (Figure 1).

Although tumors in BRCA1 mutation carriers are more frequently estrogen- and progesterone receptor negative, a clear influence on the occurrence of (contralateral) cancers has been described for hormonal factors like menopause and BPSO, and less consistently for breastfeeding, use of oral contraceptives, pregnancy, parity and tamoxifen.[22] All these hormonal influences may, like other host factors, have an impact on tumor growth rate. These factors may affect tumor growth to varying degrees between carriers of BRCA1/2 mutations and non-carriers. Within the size and scope of our study we could only account for the strongest proven hormonal influence of menopause/BPSO. Extended and different studies are needed to clarify these complex issues.

Spratt and colleagues calculated in sporadic breast cancer patients, a wide ranging DT from 10 to 7051 days with an age range 18-88 years. With age sorted into categories, they did not find a clear relationship between growth rates and age.[23] However, they assessed less fast growing tumors by not including cancers that were only visible at diagnosis. Kusama and colleagues[24] on the other hand, found significantly less tumors with short doubling times in patients age 60 years and over than in younger patients. Peer and colleagues,[18] calculated a median DT of 80 days (95% CI 44-147) for breast cancers in women less than 50 years of age who were not selected for risk, which was twice as fast as in women aged 50-70 years. These results are quite similar to the pre- and post-menopausal growth rates we calculated from non-carriers (mean 75 and 153 days, respectively), reflecting most likely the comparable ages at detection. The data available from sporadic breast cancers in the literature substantially support our current analyses.

Breast screening women aims to detect cancers at an earlier stage at which the future development of metastases is less likely, in order to possibly improve survival. Tumor size at diagnosis and the number of positive axillary nodes are strong prognostic factors for survival in sporadic and hereditary breast cancers,[4-7,25] even though other evidence suggests that the proclivity to metastasize is acquired early in tumor genesis.[3] The percentage of patients with metastases seems to increase faster with size in high grade breast cancers than in low grade.[26] Tabar et al.,[27] however, found good cumulative 12 year disease specific survival rates of over 90% of all high grade tumors ≤1 cm.

If we try to assess the optimal screening interval, taking the impact of tumor stage into account, we should consider, that a tumor with a diameter of 2 mm, missed at imaging, needs 4 doubling times to reach 5 mm, where it becomes easier to detect but is most likely still node-negative. In that period, a tumor with the same growth rate missed at 4mm may reach 1 cm. With regard to stage at detection a 4 times DT screening interval seems acceptable. In our study this would result in screening intervals of 3-7 months from age 30 till 40 years; 7-16 months from 40 till 50 years. and 16-32 months from 50 till 60 years (Figure 3), reflecting the gradual decrease in growth rate for tumors detected at increasing age. In practice, and because of the range of DTs at a given age, this might translate into a biannual screening-test before age 40 years, annual between 40 and 50 years and once every 2 years at age 50-60 years. It has been suggested by different models that in selected groups of women, biannual imaging might be necessary to improve survival.[13,19,28,29]

At such frequency, a test with high sensitivity for invasive cancer seems the method of choice. In BRCA1/2 mutation carriers, MRI seems preferable over mammography because the tumor characteristics cause frequent false-negative mammography results.[30] In MRI screening studies, sensitivity for invasive cancers proved better for MRI than mammography, but separate estimates for BRCA1/2 carriers are not yet available.[8,9] The number of BRCA1/2 mutation carriers under surveillance is relatively small and their expected tumor incidence is high (2% yearly between age 25 and 50 years).[1,2] Cost-effectiveness analyses have now been performed while impact on survival has yet to be shown.

In the large group of women at hereditary risk without a known BRCA1/2 mutation in the family, screening is usually started at an older age than in BRCA1/2 mutation carriers. Imaging annually between ages 40 and 50 years and once every 2 years between 50 and 60 years may be appropriate. This is in agreement with studies that have estimated the sojourn time (i.e., the length of time the disease is in the preclinical detectable phase) in women aged 40-49 to be 1 year.[31,32]

With 4 DCIS out of 30 cancers detected in BRCA1 carriers (and 1 in BRCA2) we cannot confirm that the in situ stage is skipped in BRCA1 cancers. With screening DCIS can be detected. We could recognize DCIS 4 times only at diagnosis, not the previous year. We do not know for how long DCIS may grow before invasion starts-the event we aim to prevent. But DCIS could reach a considerable size (33 and >40 mm, respectively) in carriers and non-carriers.

In conclusion, age at detection is the main indicator for growth rates of hereditary and familial breast cancers. If screening may prove indicated from a certain age on, the woman's age and not the risk group should determine the screening interval. A high sensitivity biannual test may be appropriate before age 40 years.

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CHAPTER 9

Discussion and concluding remarks

DISCUSSION AND CONCLUDING REMARKS

At the end of the 20th century, prospective MRI breast cancer screening studies started in women with a hereditary risk, in several countries such as The Netherlands, Canada, the United Kingdom and Germany.[1-4] In these studies women were screened by MRI and mammography in addition to clinical breast examination (CBE) and sometimes ultrasound. Through national collaboration, the Dutch MRISC study provided within 4 years meaningful data. In this thesis first outcomes of the MRISC study were described. These results are discussed in this chapter and at the end of this chapter conclusions and recommendations based on this thesis are formulated.

Aim 1. The efficacy of breast cancer screening in women with a familial or genetic predisposition

In chapter 4 and 5 we provide evidence that breast cancer screening, with a scheme consisting of a 6-monthly CBE and yearly mammography and MRI in women with a familial or genetic risk, facilitates the detection of breast cancers in an earlier stage than in symptomatic age-matched controls. The methodologically best study design to investigate if screening facilitates early breast cancer diagnosis leads to breast cancer mortality reduction is that of a randomized controlled trial, including a non-screening arm. Because of ethical reasons this was not possible (anymore) in this high risk population and therefore in the MRISC trial there was chosen for an observational prospective design with comparison of screening tests for each woman. This means that two external control groups of symptomatic breast cancer patients were used to investigate if screening facilitated early breast cancer diagnosis.

The use of an external control group in a cancer screening trial may introduce different types of bias such as:

1. Length-time bias.[5] Length-time is expected to be largest in the first round of a screening program. Therefore in this thesis characteristics of tumors detected in the subsequent rounds or in the interval after the subsequent rounds were analyzed separately (chapter 5). We found that also tumors detected during the subsequent rounds were smaller and less often lymph node positive than those in the symptomatic control groups.
2. Another bias which might occur is selection bias.[5] From other cancer screening trials in the general population we know that non-attenders can differ from attenders according to socio-economic factors. It is also suggested that non-attenders of a screening program have a worse prognosis than non-invited controls when breast cancer is diagnosed.[6] Our screening group is a group of women who is aware of their high risk for breast cancer and asks actively for breast cancer mortality risk reducing strategies by themselves. Ninety percent of the women invited to participate in the MRISC agreed. Because each external control group has its own limitations, we selected not one but two different control groups. The first control group consisted of unselected symptomatic breast cancer patients without a high risk for breast cancer. These data were obtained from the Dutch Cancer Registry. Our second control group consisted of symptomatic high risk patients, who were either not aware of their high risk or did not opt for screening (chapter 4).

3. The third common bias in cancer screening studies is lead-time bias. This type of bias may occur when breast cancer mortality is the end point of the study. In the MRISC study, as yet, the number of death events is too small and follow-up too short. Therefore, for the analyses in this thesis, tumor stage was used as a surrogate end point. Because lead-time bias may occur, it is not correct to estimate survival of the screened group and the control group from tables with tumor stage specific survival and to compare these survival rates, without any correction for lead-time.

To our knowledge, the MRISC study, described in this thesis, is currently the only MRI screening study that compared tumor characteristics of the screened group with those of age-matched symptomatic patients. The other MRI screening studies didn't compare tumor stage of tumors detected in the study with those of age-matched symptomatic patients. But also in the other MRI screening trials stages of detected tumors are favorable and comparable with the stage of tumors detected in the screening group of the MRISC study (for a review of these MRI studies see chapter 2).[2-4]

As yet, none of the screening studies in women with a hereditary risk have investigated mortality reduction because of a short-term follow-up. Therefore, mortality reduction in the MRISC study is predicted with a computer simulation model (MISCAN).[7] This model predicted a breast cancer mortality reduction of 41% in BRCA1/2 mutation carriers and 40% in the moderate risk category (15-30% cumulative lifetime risk).[8] Also when screened by mammography only, a breast cancer mortality reduction was expected (30% in the moderate risk category), but this reduction was smaller than when screened by both MRI and mammography.[8] This is in line with results of a study of Maurice et al,[9] which estimates a breast cancer mortality reduction of 24% by screening with mammography only.

In Table 1 the estimated breast cancer mortality reduction in BRCA1/2 carriers by screening is compared with the breast cancer reduction of alternative risk reducing methods as prophylactic mastectomy,[10-12] prophylactic salpingo-oophorectomy[13,14] and chemoprevention with tamoxifen.[15] Prophylactic mastectomy remains the most effective method to reduce breast cancer (mortality).

Aim 2. The value of MRI in this screening scheme compared to mammography

In chapter 4, 5, 6 and 7 evidence is provided that MRI is a more sensitive screening method than mammography. An almost twice as high sensitivity for MRI was found as for mammography (71 vs. 40%; P=0.02 for all breast cancers; 80 vs. 33%; P<0.001 for invasive cancers only). The sensitivity of CBE was relatively low (17%). These results are in line with that of similar studies of other research groups, published later on.[2-4] Although the participants of the different MRI screening studies differ with respect to hereditary risk, age and inclusion of women with previous breast cancer, all studies found an approximately two times higher sensitivity for MRI than for mammography (chapter 2). In the subsequent rounds, MRI remained a more sensitive screening method than mammography for invasive cancers (77 vs. 29%; P=0.02; chapter 5). Both the Canadian and British study published

results of the first and subsequent rounds separately.[2,3] Also in these studies, MRI remains more sensitive than mammography in the subsequent screening rounds.
In the Dutch and British study, mammography is more sensitive in detecting DCIS than MRI. In the Dutch study MRI detected one out of six cases of DCIS and mammography five out of six (chapter 4 and 6); in the British study this is for MRI two out of six cases of DCIS and for mammography five out of six cases of DCIS. These results were not in line with that of the Canadian study, where four out of six cases of DCIS are detected by MRI and this was more than by mammography (three out of six). Reasons might be differences in MRI techniques used and/or differences in experiences of radiologists.[16] Most importantly these possible reasons, in all studies number of cases of DCIS are too small for a robust statistical analysis and firm conclusions.

Table 1. Risk reduction estimates for BRCA1/2 mutation carriers by different preventive strategies.

	Breast cancer reduction
Tamoxifen[15]	40%
Prophylactic salpingo-oophorectomy[13,14]	50%
Prophylactic salpingo-oophorectomy + tamoxifen	70% (?)
Prophylactic mastectomy[10-12]	90-100%
	Breast cancer mortality reduction
Regular screening by mammography + MRI[8,39]	40%

In addition to comparing the sensitivity of MRI and mammography, we also assessed value of MRI screening when added to a standard screening scheme consisting of mammography and CBE. Twenty (40%) of all 50 detected breast cancers were detected by MRI-only and thus missed by mammography and clinical breast examination (chapter 4 and 6). In BRCA1/2 mutation carriers 10 (43%) of the in total 23 detected cancers in this group were detected by MRI only and missed by mammography and CBE. MRI appeared to be a cost-effective screening method in BRCA1/2 mutation carriers, also in addition to mammography and CBE screening, for women aged 30-60 years.[8] In the moderate risk group MRI screening appeared to be cost-effective compared to no screening, but cost-effectiveness of MRI instead of mammographic screening or in addition to mammographic screening was questionable. Mammography was less sensitive than MRI, but can detect cancers not detected by MRI, especially DCIS. In the MRISC study mammography detected eight cancers (4x DCIS) missed by MRI, of which six cancers were also missed by CBE.
Although MRI was a more sensitive screening method than mammography in women with a hereditary risk, it was less specific than mammography (90 vs. 95% respectively). This difference in specificity decreased, but remained in the subsequent rounds (92 vs. 95% respectively) (chapter 4 and 5). This means that about two times more additional investigations were performed as a result of MRI than as a result of mammography. More than three times as many "unnecessary" biopsies were performed after a positive MRI than after a positive mammography. Fifty-six biopsies were performed after a positive MRI, of which 24 were negative. The number of biopsies after a positive mammography was 25 of

which 7 were negative. Consequently, the positive biopsy rate was higher after a positive mammography (72%) than after a positive MRI (57%). The positive predictive value was comparable for mammography and MRI (8.0 vs. 7.1%) (chapter 4). Except for the study of Kuhl et al., all MRI screening studies report a lower specificity of MRI than of mammography (chapter 2). This lower specificity is an important limitation of MRI screening. However, when we combined sensitivity and one minus specificity (false positive rate) in the receiver operating characteristic (ROC) curves we found a significant higher area under the curve for MRI, meaning that MRI was a more accurate screening method than mammography in this group of high risk women.

In chapter 4, 5 and 6 we have investigated sensitivity and specificity of mammography and MRI for the whole study population. It has to be noticed that sensitivity and specificity of a test can depend on the characteristics of the population in which the test is performed. In chapter 7 was found, as expected from earlier studies in the general population,[17-20] that sensitivity of mammography was independently decreased in younger women, pre-menopausal women, women with a BRCA1 or BRCA2 mutation and women with a high breast density. For MRI the independent trends of age, menopausal status and hereditary risk on sensitivity were less clear than for mammography. This means that MRI screening has probably the highest additional value to mammographic screening in mutation carriers and young and pre-menopausal women. Unexpected was the finding that a high breast density was significantly associated with a decreased sensitivity of MRI. Thus the hypothesis that MRI has the most additional value to mammography in women with a high breast density was not confirmed in this thesis.

Recently there is evidence provided that digital mammography is more accurate than conventional (screen-film) mammography in women younger than 50 years, pre-menopausal women and women with dense breast tissue.[21] This may result in a less obvious difference between mammography and MRI in these groups when digital mammography is used.

A decreased sensitivity in BRCA1/2 mutation carriers was only found for mammography and not for MRI. This suggests that MRI was most superior to mammography in BRCA1/2 mutation carriers, as shown by the ROC curves in chapter 7. Possible reasons for the lower sensitivity of mammography in mutation carriers, after correction for menopausal status or age and breast density, are atypical mammographic features[22] and a higher tumor growth rate.

In chapter 8 we have investigated the tumor growth rate, expressed in tumor doubling time, for BRCA1/2 mutation carriers as compared with high risk women without a proven BRCA1/2 mutation. We found a mean tumor doubling time of 45 days in women with a BRCA1/2 mutation in contrast to 84 days (ratio 0.5) in women without a BRCA1/2 mutation (P=0.048). However, when adjusted for age and menopausal status, this difference decreased (ratio 0.7 (95% CI 0.4-1.30) for BRCA1/2 vs. non-BRCA1/2 mutation carriers). Although this finding was not statistically significant anymore, a trend for a higher tumor growth rate in BRCA1/2 mutation carriers remained. An independent correlation between a BRCA1/2 mutation and tumor doubling time was expected, because BRCA1/2-related tumors have a higher mitotic activity index (MAI), also when adjusted for age.[23,24] However, the correlation between MAI and tumor doubling time was not investigated in that same series. The relation

between a BRCA1/2 mutation and tumor growth rate should be further studied in larger series, preferentially separated for women with a BRCA1 and BRCA2 mutation. We found a clear relation between a younger age at diagnosis and an increased tumor doubling time (ratio 1.9 per 10 year older age (95% CI 1.1-3.4) per 10 years older age) (chapter 8). This relation between age and doubling time was known from previous studies.[25,26]
For a group with a higher tumor growth rate a more frequent screening may be considered. Therefore when screening is performed before the age of 50, a yearly interval is recommended in contrast to an interval of 2 years in the protocol for screening in the general population in women aged 50-75 years.[27] A shorter than yearly interval is currently not advised for mammography: the sensitivity of mammography is limited in young women, especially for those with dense breasts, and a more than yearly frequency means a greater exposure to radiation of the breasts. MRI more than once a year, with its high costs and relatively low specificity might only be effective in a well defined small group with a very high incidence of breast cancer and a fast tumor growth rate. Currently, such a group is not identifiable, because it has not yet been defined. Further, the feasibility and cost-effectiveness of such an intensive screening scheme must be carefully investigated.

ULTRASOUND AS SCREENING TOOL

In the Dutch MRISC study, described in this thesis, only mammography, MRI and CBE were performed as screening tools. Ultrasound was only performed as additional imaging tool in case of abnormalities found by mammography, MRI or CBE. In the Canadian[2] and German[4] studies ultrasound was used as standard screening tool in addition to mammography and MRI. The sensitivity of ultrasound in both studies was comparable with that of mammography and thus lower than that of MRI. Also the sensitivity of the combination of ultrasound and mammography (55% in the Canadian and 48% in the German study) was lower than that of MRI (77% and 91%, respectively). The specificity of ultrasound in the study of Warner was 96%, which was comparable with that of MRI (95%) and lower than that of mammography (99.8%). In the study of Kuhl specificity of ultrasound (91%) was lower than that of both mammography (97%) and MRI (97%). These results suggest that there is no role for ultrasound as standard screening tool in women with a familial or genetic predisposition.

ADVANTAGES AND DISADVANTAGES OF MRI SCREENING COMPARED TO MAMMOGRAPHIC SCREENING

Before a new screening tool is recommended, advantages and disadvantages should be carefully considered. The present and other MRI screening studies in women with an increased risk show that MRI has a far better sensitivity than mammography. This comes at a price of a lower specificity, causing extra costs and possibly anxiety. Other disadvantages of MRI are pointed out in chapter 2 and include patient groups in whom performing of MRI is not possible and the time and costs that accompany the performance of an MRI scan. Further disadvantages of MRI are that neither the technique nor the interpretation is standardized.[28]

Although MRI caused more anxiety than mammography, MRI is preferred as screening tool over mammography by women with an increased risk.[29]

An advantage of MRI compared to mammography is the absence of exposure to (low-dose) radiation. Studies in atomic bomb survivors and women exposed to radiation for diagnostic or treatment reasons, such as women treated for Hodgkin's disease, found that radiation is a risk factor for breast cancer.[30,31] During screening for breast cancer radiation doses are much lower than in atomic bomb survivors or women treated for Hodgkin's disease. It is still unknown how big the problem of radiation induced tumors is, but model studies suggest that it is a minor problem in women 50-75 years with an average risk.[32] However, it is suggested that breast tissue of young women is more sensitive to radiation risk.[32,33] The risk of radiation exposure in BRCA1/2 mutation carriers is unclear. While tumors deficient in BRCA1 or BRCA2 show increased sensitivity to ionizing radiation, several in vitro studies of BRCA1 and BRCA2 mutation carriers failed to show increased radiosensitivity.[33-36] Results of exposure to low-dose ionizing radiation and breast cancer in BRCA1/2 mutation carriers are inconsistent. A case control study found that exposure to chest X-ray is associated with an increased risk of breast cancer in BRCA1/2 mutation carriers. The estimated risk increased with an exposure at a younger age, particularly when exposed before the age of 20 years.[37] However, screening in BRCA1/2 mutation carriers started most times at an age of 25 years. Furthermore, a limitation of this study[37] is that results might (partly) be explained by recall bias. Another case-control study found that exposure to screening mammography of BRCA1/2 mutation carriers is not associated with an increased risk of breast cancer, also when started with screening before the age of 30.[38] More research to the association between exposure to low-dose radiation, the age of this exposure and breast cancer risk in BRCA1/2 mutation carriers is warranted.

CONCLUSIONS AND RECOMMENDATIONS

The current screening guidelines in the Netherlands for three different genetic risk groups are summarized in Table 2. Guidelines can differ between different countries as a consequence of differences in facilities and reimbursement, but also in the Netherlands there might be some small differences between different familial cancer clinics. For the genetic groups in which yearly mammography is recommended until age 50 or 60, after this age a two yearly mammography in the nation wide screening program for the general population until age 75 is advised.

In BRCA1/2 mutation carriers the incidence of breast cancer is high. This makes the cost-effectiveness of an intensive screening program consisting of yearly MRI and mammography and 6-mothly CBE favorable.[8,39] In the Netherlands, there is consensus that MRI should be offered as a standard screening tool to all BRCA1/2 mutation carriers, in addition to mammography and CBE. While there is some discussion about the optimal start and end age of MRI screening, MRI screening is most times recommended in BRCA1/2 mutation carriers in the age group from 25 to 60 years (Table 1). Although preventive mastectomy is the most effective method to reduce the risk of breast cancer (mortality) in BRCA1 and BRCA2

mutation carriers, MRI screening is a good alternative for mutation carriers for whom preventive mastectomy is unacceptable. Both risk reducing strategies, prophylactic mastectomy and screening by MRI, should be offered as an option to BRCA1/2 mutation carriers, in addition to the option of prophylactic salpingo-oophorectomy.
In the high risk group (cumulative lifetime risk of 30-50%) the incidence of breast cancer is lower than in mutation carriers, which makes cost-effectiveness of MRI screening less favorable for the high risk group. However, we observed in this high risk group that the incidence of breast cancer was not higher than in the moderate risk group (cumulative lifetime risk of 15-30%). In contrast to this finding, in practice and in the literature it is possible to identify families with a very high risk. Therefore in a part of this genetic risk group with the highest risk, MRI screening is probably cost-effective. Further research to the real risk and the most optimal screening scheme is recommended for this group. Currently, screening by MRI should preferably be offered in a research setting.

Table 2. Current breast cancer screening guidelines for three different genetic risk groups.

	Mutation carriers 50-85% CLTR	High risk group 30-50% CLTR	Moderate risk group 15-30% CLTR
CBE			
Start age	25	25	35
End Age	75	60	50
Mammography (yearly)			
Start age	25	25	35
End age	75	60	50
MRI (yearly)			
Start age	25	Preferably in a research setting	
End age	60		

CLTR: cumulative lifetime risk, CBE: clinical breast examination.

In the moderate risk group (cumulative lifetime risk of 15-30%) MRI was also a more accurate screening method than mammography. However, the lower incidence of breast cancer in this moderate risk group as compared to mutation carriers, resulting in a less favorable cost-effectiveness of MRI, and the higher sensitivity of mammography in this group compared to mutation carriers, makes the added value of MRI screening less pronounced in this group. A longer follow-up in this genetic risk group is needed for more definitive conclusions about MRI screening. Until these data are available MRI screening should preferably be offered in a research setting.

Comments and considerations according to the current screening guidelines:

- Breast cancer screening in women with a genetic or familial predisposition needs a different organization than screening offered in nation wide programs for the general population. Although clinical breast examination has a low sensitivity when performed in a screening program that also includes mammography and MRI, a clinical visit is advisable for different other reasons, for example updating of family history about breast

cancer, psychological counseling, discussing other preventive strategies, lifestyle, possible problems and new developments and new opinions. The frequency of CBE might be reduced to once a year during long-term follow-up, especially in the genetic risk groups without a proven mutation.

- In some cases, mammography can detect tumors occult at MRI. Probably, the value of mammography in addition to MRI is most important for detecting DCIS. However, inconsistent results between different studies are found and larger series are needed to investigate the role of mammography and MRI in detecting DCIS. Also more research is needed to possibly reduce the frequency of mammography in case of MRI screening. Screening schemes with alternative uses of MRI and mammography are also valuable to investigate.
- Effectiveness and cost-effectiveness for different screening schemes will possibly be more favorable when also other risk factors are taken in account than only the family history. For example dense breast tissue, fibrocystic mastopathy, atypical hyperplasia, hormonal factors etc. Therefore, some flexibility according to the choice of the screening scheme by the physician is advisable.
- The follow-up in the study described in this thesis was short (almost 3 years) and conclusions were based on a small number of diagnosed breast cancers (50 cases). Currently, the MRISC study is continued to at least January 2008 and a pooled analysis with data of the Dutch, British and Canadian study is planned. Research questions are to obtain long-term and more precise effect estimates and to draw more statistically proven conclusions for the different genetic risk groups. In addition, an important objective is the development of more specific guidelines for subgroups according to different ages, menopausal status and breast density. Continuation of the MRI screening studies is also important to adequately assess breast cancer mortality reduction. As a result of new study findings, insights and discussions, it is possible that in the future the current guidelines will be adapted.
- Although MRI is already recommended as a screening method in BRCA1/2 mutation carriers and still under investigation in other high risk women, further research into the improvement of the accuracy and especially the specificity of MRI is important. Computer-aided diagnosis might play a role in the improvement of the accuracy of MRI.[40] On the long term molecular biological diagnostic tools may appear to be valuable for the early diagnosis of breast cancer.[41]

The results of the MRISC study and the guidelines described above, are also described in a report for the Dutch Health and Insurance Council.[42] The Dutch Health and Insurance Council agreed with our recommended guidelines as stated in the report and urges into implementation of these guidelines in the Netherlands. Implementation is done via the HEBON (Hereditary Breast and Ovarian Cancer in the Netherlands) group, the Dutch societies for clinical genetics, oncology and radiology, and the family cancer clinics.

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SUMMARY

Women with a strong family history of breast and/or ovarian cancer combined with young ages at diagnosis of affected family members have an increased risk of these types of cancer. In 1994 and 1995 respectively, the BRCA1 and BRCA2 genes were identified. A germline mutation in one of these genes is associated with very high risks of early onset breast and ovarian cancer.

Current options for BRCA1/2 mutation carriers to reduce their risk of breast cancer or death by breast cancer include prophylactic mastectomy, prophylactic salpingo-oophorectomy, chemoprevention and screening. Screening for breast cancer is also offered to women with a familial predisposition, but without a proven BRCA1/2 mutation. Several studies have investigated the efficacy of mammographic screening, sometimes in combination with clinical breast examination (CBE)) in high-risk groups of women. However, the efficacy of mammography screening has never been clearly demonstrated. Sensitivity of mammography was low this group of women in comparison with post-menopausal women screened in population based studies, most likely because of the young screening age of and consequently frequent a high density of the breast tissue. MRI appeared to be a sensitive method for detection of breast cancer in a diagnostic setting. For this reason, in the late nineties several breast cancer screening studies comparing the value of MRI and mammography were set up in women with a genetic susceptibility. Results of pilot and preliminary studies showed in all of them a very high sensitivity of MRI, while sensitivity of mammography was never higher than 50%. Recently, the first results of four large prospective studies were published, among which the Dutch national MRISC study. In this thesis, the short-term results of the MRISC study are described. Two of the main objectives of the MRISC study are addressed in this thesis:

1. Assessment of the efficacy of screening in diagnosing early-stage breast cancer in women with a familial or genetic predisposition
2. Assessment of the value of MRI in this screening scheme compared to mammography

In Chapter 3 the design of the MRISC study is described. The start date of this study was 1 November, 1999, and 6 cancer centers and university hospitals participated in this study. In these centers, women who were already under intensive surveillance and women who came for screening for the first time were asked by a clinician to participate in the study. The inclusion criteria for participation were a cumulative lifetime risk of breast cancer of >15% due to a familial or genetic predisposition, an age between 25 and 70 years, or younger than 25 in women from families with a very young age of onset (<30 years). Women with previous breast cancer or symptoms of breast cancer were excluded. The participants visited the hospital twice a year for a clinical breast examination and once a year for a mammography and MRI, with a maximum period of 6 weeks between both imaging modalities. Mammography and MRI were independently evaluated.

Breast cancer detection rates, screening parameters of mammography and MRI, and characteristics of tumors diagnosed in the MRISC study are described in Chapter 4. In total 1909 eligible women were entered in the MRISC study, including 358 carriers of a germline mutation. During a median follow-up time of 2.9 years, 51 tumors were detected, of which 1 lymphoma, 44 invasive breast cancers and 6 ductal carcinomas in situ (DCIS). The detection rate for breast cancer was 9.5 per 1000 women-years at risk, with the highest detection rate for mutation carriers (26.5 cancers per 1000 women-years at risk). MRI was a more sensitive screening method than mammography (71.8% vs. 33.3%, respectively); the sensitivity of clinical breast examination was only 17.9%. However, mammography was more sensitive than MRI for detecting DCIS: mammography detected 5 out of 6 cases of DCIS, MRI only one out of 6. Overall, the specificity was higher for mammography (95.0%) than for MRI (89.8%); the specificity for clinical breast examination was 98.1%. Sensitivity and specificity were combined in a receiver operating characteristic (ROC) curve. The area under the curve for MRI was significantly higher than for mammography, meaning that MRI can better discriminate between women with and without breast cancer.
Characteristics of tumors detected in the screened group were compared with those of two age-matched symptomatic control groups. Tumors detected in the MRISC study were detected in a more favorable stage than those of the symptomatic controls, they were more often ≤1 cm (43.2 vs. 14.0% ($P<0.001$) and 12.5% ($P=0.04$) in both control groups, respectively, and the incidence of positive lymph nodes was lower in the MRISC study group (21.4%) compared to 52.4% ($P<0.001$) and 56.4% ($P=0.001$) in the two control groups.

Screening parameters and tumor characteristics can differ between the first round and subsequent rounds of a screening program. In the MRISC study, yearly MRI is added to the existing screening program of yearly mammography and 6-monthly clinical breast examination. This means that the results described in chapter 4 are mainly based on comparing a first MRI with a mammography after a prior mammography. As a result the differences in sensitivity and specificity between MRI and mammography might be overestimated. In chapter 5 we have described whether the differences in sensitivity and false positive rate between MRI and mammography as observed in chapter 4 are maintained in the subsequent rounds. Although we observed the highest difference in both sensitivity and false positive rate between MRI and mammography in the first round, also in the subsequent rounds these statistically significant differences between MRI and mammography remained with respect to screening parameters: 76.5% (MRI) vs. 29.4% (mammography) $P=0.02$ for sensitivity, 8.2% (MRI) vs. 4.6% (mammography); $P<0.001$ for the false positive rate.
No major differences with respect to tumor stage were found between tumors detected at the subsequent rounds in comparison with those detected in the first round. In the subsequent rounds tumor characteristics remained more favorable with respect to size and lymph node involvement than in symptomatic age-matched controls. Because results of these subsequent rounds were possibly most predictive for long-term effects, it is expected that on the long-term this screening program will ultimately contribute to a decrease of breast cancer mortality.

In chapter 6 we investigated more in detail the contribution of MRI in the early detection of breast cancer reported in chapter 4. We did this by investigating the number and percentage of tumors that were detected by MRI and missed by mammography and by comparing tumor characteristics of MRI-only detected tumors with those of other screen-detected tumors. Forty-five of the 50 detected breast cancers were evaluable for detection method and were included in the analysis of chapter 6. Twenty-two (49%) of the 45 breast cancers were detected by MRI and were not visible at mammography, of which 20 (44%) were also not palpable (MRI-only detected tumors). Eight breast cancers (18%) were detected by mammography and not visible on MRI, 10 (22%) breast cancers were detected by both MRI and mammography. One breast cancer was only detected by clinical breast examination and missed by mammography and MRI, and 4 (9%) were detected in the interval between two screening visits. The MRI-only detected tumors were more often ≤1 cm than all other screen-detected cancers (58 vs. 31%; P=0.11). Also MRI-only detected tumors were more often node-negative than other screen detected cancers (94 vs. 59%; P=0.02). This suggests that MRI importantly contributes to the early detection of breast cancer, as described in chapter 4.

Whether age, a BRCA1/2 mutation, menopausal stage and breast density independently influenced sensitivity and false positive rate (1-specificity) of mammography and MRI is investigated in Chapter 7. An unexpected finding was that sensitivity of MRI was significantly decreased in women with a high mammographic breast density compared to women with a low breast density (adjusted OR (OR_{adj}) 0.08 [95% CI 0.01-0.84]). As expected, also the sensitivity of mammography was decreased by a high breast density, but not significantly (OR_{adj} 0.42 [95% CI 0.10-1.7]). Further there were non-significant trends of a decreased sensitivity of mammography in younger and pre-menopausal women and in women with a BRCA1/2 mutation. These trends were not observed for MRI. False-positive rates of both mammography (OR_{adj} 1.67 [1.22-2.28]) and MRI (OR_{adj} 1.21 [0.97-1.51]) were increased by high breast density, that of MRI by pre-menopausal status (OR_{adj} 1.70 [1.23-2.36]), young age (OR_{adj} 1.58 [1.17-2.13]) for women 40-49 years versus women ≥50 years).

In chapter 8, the tumor growth rate of 30 tumors detected in BRCA1/2 mutation carriers is compared with the growth rate of 25 tumors detected in women with a familial or genetic risk, but no proven BRCA1/2 mutation. An exponential tumor growth was expected and growth rate was expressed in tumor volume doubling time. Tumor size was measured on either MRI or mammography. The tumor volume doubling time was 45 days (95% CI 26-73 days) in BRCA1/2 mutation carriers and this was significantly shorter (P=0.048) than in women without a proven mutation, in which the tumor volume doubling time was 84 days (95% CI 58-131 days) (ratio 0.5). However, when this result was adjusted for age and menopausal status, there was only a non-significant trend for a faster tumor volume doubling time in mutation carriers compared to non-mutation carriers (adjusted ratio 0.7 [95% CI 0.4-1.3]). Only a higher age significantly prolonged tumor volume doubling time (adjusted ratio 1.9 per 10 years older age [95% CI 1.1-3.4]).

In chapter 9 results described in this thesis are discussed and conclusions are summarized. Further, recommendations for screening of this group and for further research were done. The overall conclusion was that MRI is a more sensitive screening method than mammography, but less specific. MRI is a more accurate method and can better discriminate between women with and without breast cancer. Screening by the scheme used in the MRISC study (yearly mammography and MRI and 6-monthly breast examination) facilitated an early breast cancer diagnosis. Therefore, in the current screening guidelines for BRCA1/2 mutation carriers, yearly MRI is added to the previously used screening scheme of yearly mammography and 6-monthly clinical breast examination. In women with an increased risk but without a proven BRCA1/2 mutation, the breast cancer incidence is lower and the sensitivity of mammography is better than in gene mutation carriers, causing a less favorable cost-effectiveness for the addition of MRI. Therefore, for this group of women, currently there is no consensus whether MRI has to be advised as standard screening tool and MRI screening should preferably be performed in a research setting. An important research question for the future is whether high-risk women without a proven BRCA1/2 germline mutation should be screened by MRI, and what should be their minimum genetic risk and age at entry.

SAMENVATTING

Vrouwen bij wie borstkanker en/of ovariumkanker veelvuldig in de familie voorkomt hebben een verhoogde kans op het krijgen van deze soorten kanker, vooral als deze soorten kanker bij hun familieleden op jonge leeftijd zijn gediagnosticeerd. In 1994 en 1995 zijn er twee borstkankergenen geïdentificeerd, de zogenaamde BRCA1 en BRCA2 genen. Bij een kiembaanmutatie in één van deze genen is er een hoog risico op het krijgen van borstkanker en ovariumkanker op een relatief jonge leeftijd. Huidige opties voor BRCA1/2 genmutatiedraagsters om de kans op (sterfte aan) borstkanker te verlagen zijn onder andere profylactische mastectomie, profylactische salpingo-ovariectomie, chemopreventie en screening. Ook aan vrouwen met een verhoogd familiair risico op borstkanker, maar zonder bewezen genmutatie, wordt screening aangeboden als optie.
In een aantal studies is onderzocht of screening met mammografie, al dan niet in combinatie met klinisch borstonderzoek, effectief is bij deze groep vrouwen met een hoog risico. De effectiviteit is nooit duidelijk aangetoond. De sensitiviteit van de mammografie was laag, door de jonge leeftijd van de vrouwen bij screening en daarmee veelal de hoge dichtheid van het borstklierweefsel in vergelijking met post-menopausale vrouwen gescreend in populatiegebaseerde studies. Omdat MRI in een diagnostische setting een sensitieve methode bleek om borsttumoren te ontdekken, zijn eind jaren 90 in een aantal landen studies van start gegaan die de effectiviteit van MRI screening vergeleken met die van mammografie screening bij vrouwen met een verhoogd risico. Resultaten van de eerste pilot en preliminaire studies lieten een hoge sensitiviteit zien van de MRI, terwijl de sensitiviteit van de mammografie in geen van deze studies boven de 50% kwam. Op dit moment zijn de eerste resultaten van vier grote prospectieve studies gepubliceerd, waaronder die van de Nederlandse MRISC studie. In dit proefschrift worden de korte termijn resultaten van de MRISC studie beschreven. Twee van de hoofdvragen van de MRISC studie staan hierbij centraal:

1. Kan door screening bij vrouwen met een familiaire of genetische predispositie borstkanker in een eerder stadium worden ontdekt
2. Wat is de waarde van de MRI bij deze screening in vergelijking met de mammografie

In hoofdstuk 3 wordt het design van de MRISC studie beschreven. Deze studie is 1 november 1999 van start gegaan. Zes kankercentra en universitair medische centra deden mee aan de studie. In deze centra werden vrouwen die al onder controle stonden voor de borsten of die voor de eerste keer voor screening kwamen, door een arts gevraagd mee te doen met de MRISC studie. De inclusiecriteria waren een levenslang risico voor borstkanker van ≥15% vanwege een familiaire of genetische predispositie, een leeftijd tussen de 25 en 70 jaar, of jonger dan 25 voor vrouwen uit families waar borstkanker al voor het 30ste jaar voorkomt. Vrouwen die al eerder borstkanker hadden gehad of symptomen verdacht voor borstkanker hadden, werden geëxcludeerd. De vrouwen die meededen kwamen 2x per jaar voor klinisch borstonderzoek, daarnaast werd 1x per jaar een MRI en mammografie gemaakt, met een maximale periode van 6 weken tussen beide onderzoeken. De MRI en mammografie werden onafhankelijk van elkaar beoordeeld.

Het detectiecijfer voor borstkanker, screeningsparameters van mammografie en MRI en de karakteristieken van de tumoren gevonden in de MRISC studie worden beschreven in hoofdstuk 4. In totaal hebben 1909 vrouwen deelgenomen aan de MRISC studie, waarvan 358 draagsters van een kiembaanmutatie. Bij een mediane follow-up tijd van 2,9 jaar werden bij deze vrouwen 51 tumoren gedetecteerd, waarvan één lymfoom, 44 invasieve borsttumoren en 6x ductaal carcinoma in situ (DCIS), een voorstadium van borstkanker. Het detectiecijfer voor borstkanker was 9,5 per 1000 vrouwjaren met het hoogste detectiecijfer voor mutatiedraagsters, namelijk 26,5 per 1000 vrouwjaren. We hebben gevonden dat MRI een meer sensitieve screeningsmethode is dan mammografie, MRI ontdekte 71,8% van de tumoren en mammografie 33,3% terwijl de sensitiviteit van klinisch borstonderzoek maar 17,9% was. Voor DCIS was mammografie meer sensitief dan MRI, mammografie ontdekte 5 van de 6 DCIS gevallen, MRI slechts één van de 6. De specificiteit was voor mammografie hoger dan voor MRI (95,0% vs. 89,8%), voor klinisch borstonderzoek was deze 98,1%. Sensitiviteit en specificiteit werden tegen elkaar uitgezet in de zogenaamde receiver operating characteristic (ROC) curve. De oppervlakte onder de curve voor MRI was significant hoger dan voor mammografie, hetgeen betekent dat MRI een beter onderscheid maakt tussen mensen met en zonder maligniteit.
De karakteristieken van tumoren gevonden in deze gescreende groep werden vergeleken met tumorkarakteristieken van twee symptomatische controlegroepen. De tumoren gevonden in de MRISC studie werden in een gunstiger stadium gevonden dan de tumoren in de beide symptomatische controle groepen. Ze waren vaker ≤1 cm (43,2 vs. 14,0% (P<0,001) en 12,5% (p=0,04) in de beide controlegroepen) en hadden minder vaak positieve lymfeklieren (21,4 vs. 52,4% (P<0,001) en 56,4% (P=0,001) in de controlegroepen).

Screeningsparameters en tumorkarakteristieken kunnen verschillen tussen de eerste en de vervolgrondes in een screeningsprogramma. In de MRISC studie is een jaarlijkse MRI toegevoegd aan het reeds bestaande schema met mammografie en klinisch borstonderzoek. Dit betekent dat in de eerste ronde vaak het resultaat van een eerste MRI wordt vergeleken met een mammografie na een eerdere mnammografie. Hierdoor kan het verschil in sensitiviteit en specificiteit tussen mammografie en MRI overschat worden. Daarom beschrijven we in hoofdstuk 5 resultaten van een studie waarbij onderzocht werd of de hogere sensitiviteit en percentage vals-positieven (1-specificiteit) van MRI vergeleken met mammografie zoals gevonden in hoofdstuk 4 ook in de vervolgrondes te zien is.
Alhoewel het verschil in sensitiviteit en percentage vals-positieven tussen MRI en mammografie het grootst is in de eerste ronde, blijven ook in de vervolgrondes deze statistisch significante verschillen bestaan: 76,5% vs. 29,4% (P=0,02) voor sensitiviteit en 8,2% vs. 4,6% (P<0,001) voor percentage vals-positieven. Karakteristieken van tumoren ontdekt in de verschillende rondes zijn niet significant verschillend van elkaar. In de vervolgrondes blijven de karakteristieken van de detecteerde tumoren dan ook gunstiger met betrekking tot grootte en lymfeklierinvasie in vergeling met de tumorkarakteristieken van de symptomatische controlegroepen van vergelijkbare leeftijd. Omdat resultaten van de vervolgrondes mogelijk meer voorspellend zijn voor de langetermijneffecten, verwachten we

dat dit screeningsprogramma zal bijdragen aan een afname van de borstkankersterfte in deze groep vrouwen met een hoog risico op borstkanker.

In hoofdstuk 6 is meer gedetailleerd nagegaan wat de bijdrage van de MRI is in de vroegdetectie van borstkanker, welke in hoofdstuk 4 is beschreven. Dit hebben we gedaan door het aantal en percentage tumoren die met MRI zijn gedetecteerd en zijn gemist met mammografie te bepalen en vervolgens door karakteristieken van tumoren, welke alleen met MRI waren gevonden, te vergelijken met die van andere door middel van screening gedetecteerde tumoren. Van de in totaal 50 borstkankers waren er 45 evalueerbaar voor de detectiemethode en deze werden dus geïncludeerd in de analyse beschreven in hoofdstuk 6. Tweeëntwintig (49%) van de 45 borstkankers werden gevonden door MRI, maar zijn gemist met mammografie; 20 (44%) werden ook met het klinisch borstonderzoek gemist ("MRI-alleen gedetecteerde tumoren"). Acht borstkankers (18%) werden met mammografie gevonden en waren niet op de MRI te zien, 10 borstkankers (22%) waren zowel op mammografie als MRI te zien. Verder werd één borstkanker alleen met klinisch borstonderzoek gevonden en dus gemist op mammografie en MRI en 4 borstkankers (9%) werden gevonden in het interval tussen twee poliklinische controles. De MRI-alleen gedetecteerde tumoren waren vaker ≤1 cm dan alle andere screengedetecteerde borstkankers (58 vs. 31%; P=0,11). Ook hadden de MRI-alleen gedetecteerde tumoren vaker negatieve oksellymfeklieren dan alle andere screengedetecteerde tumoren (94 vs. 59%; P=0,02). Dit suggereert dat MRI een belangrijke bijdrage levert aan de vroegdetectie van tumoren die in hoofdstuk 4 beschreven is.

De invloed van leeftijd, een BRCA1/2 genmutatie, menopausale status en borstklierdichtheid op de sensitiviteit en het percentage vals-positieven (1-specificiteit) van de MRI en mammografie is beschreven in hoofdstuk 7. Een onverwachte bevinding was dat de sensitiviteit van de MRI significant lager was bij vrouwen met een hogere dichtheid van het borstklierweefsel in vergelijking met vrouwen met een lage dichtheid van het borstklierweefsel (gecorrigeerde OR 0,08 [95% betrouwbaarheidsinterval (BI) 0,01-0,84]). Zoals verwacht was ook de sensitiviteit van mammografie lager bij vrouwen met een dichter borstklierweefsel (gecorrigeerde OR 0,42 [95% BI 0,10-1,7]), maar deze bevinding was niet significant. Verder werden er niet significante trends gevonden dat sensitiviteit van de mammografie lager was bij jongere vrouwen, pre-menopausale vrouwen en vrouwen met een BRCA1/2 mutatie. Deze trends werden niet waargenomen voor MRI. Het percentage vals-positieve bevindingen van zowel mammografie (gecorrigeerde OR 1,67 [95% BI 1,22-2,28]) en MRI (gecorrigeerde OR 1,21 [95% BI 0,97-1,51]) was verhoogd bij vrouwen met een hoge dichtheid van het borstklierweefsel en dat van MRI ook bij pre-menopausale vrouwen (gecorrigeerde OR 1,70 [95% BI 1,23-2,36]) en bij jonge vrouwen (gecorrigeerde OR 1,58 [95% BI 1,17-2,13] voor vrouwen 40-49 jaar; gecorrigeerde OR 1,28 [95% BI 0,95-1,73] voor vrouwen jonger dan 40 jaar).

De tumorgroeisnelheid van 30 tumoren gedetecteerd bij BRCA1/2 mutatiedraagsters wordt in hoofdstuk 8 vergeleken met de tumorgroeisnelheid van 25 tumoren gedetecteerd bij hoogrisico vrouwen zonder bewezen BRCA1/2 mutatie. Er werd aangenomen dat de tumorgroei exponentieel plaatsvindt en deze werd dan ook in tumorvolumeverdubbelingstijd uitgedrukt. De tumorgrootte werd gemeten of op de MRI of op de mammografie. De tumorvolumeverdubbelingstijd van BRCA1/2 mutatiedraagsters was 45 dagen (95% betrouwbaarheidsinterval 26-73 dagen) en deze van de hoogrisico vrouwen zonder bewezen BRCA1/2 mutatie 84 dagen (95% BI 58-131 dagen) (ratio 0,5), dit verschil is statistisch significant (P=0,048). Echter wanneer deze resultaten voor leeftijd en menopausale status worden gecorrigeerd, is er alleen een niet significante trend dat de verdubbelingstijd van tumoren bij mutatie draagsters groter is dan die van tumoren bij niet-mutatiedraagsters (gecorrigeerde ratio 0,7 (95% BI 0,4-1,3)). Een hogere leeftijd gaat gepaard met de significante verhoging van tumorvolumeverdubbelingstijd (gecorrigeerde ratio 1,9 per leeftijdsperiode van 10 jaar (95% BI 1,1-3,4)).

In hoofdstuk 9 worden de resultaten die zijn beschreven in dit proefschrift bediscussieerd en worden er conclusies getrokken. Verder worden er aanbevelingen gedaan voor de screening van deze groep vrouwen met een verhoogd risico en voor vervolgonderzoek. Een belangrijke conclusie is dat MRI een sensitiever maar minder specifieke screeningsmethode is dan mammografie. MRI is wel meer accuraat en kan dus beter onderscheid maken tussen vrouwen met en zonder borstkanker. Screening met het in de MRISC studie gebruikte screeningsschema (6-maandelijks klinisch borstonderzoek en jaarlijkse mammografie en MRI) kan ervoor zorgen dat tumoren in een vroeg stadium worden ontdekt. Voor BRCA1/2 mutatie draagsters is in de huidige richtlijnen toepassing van de MRI toegevoegd aan het vorige screeningsschema van 2x per jaar klinisch borstonderzoek en 1x per jaar mammografie. Bij vrouwen met een verhoogd risico maar zonder een bewezen BRCA1/2 mutatie is de borstkankerincidentie lager en de sensitiviteit van de mammografie beter, waardoor de kostenbaten verhouding voor het toevoegen van MRI minder gunstig is dan bij genmutatiedraagsters. Voor deze vrouwen is er op dit moment nog geen consensus dat MRI als standaard screeningsmethode moet worden toegepast en deze vrouwen zouden bij voorkeur in onderzoeksverband met MRI gescreend moeten worden. Belangrijke vragen voor vervolgonderzoek zijn dan ook: 1) zou een deel van deze hoogrisico vrouwen zonder BRCA1/2 kiembaanmutatie met MRI moeten worden gescreend 2) wat zou dan hun minimum risico op het krijgen van borstkanker moeten zijn, en 3) op welke leeftijd moet worden begonnen met screening.

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CURRICULUM VITAE

Mieke Kriege was born on 28 January 1976 in Wassenaar, The Netherlands. After graduation in 1994 from secondary school (VWO at the Adelbert College, Wassenaar), she started her study Human Nutrition at the Wageningen University. As a part of the study, she conducted two different research projects of both 5 months at the department of Human Nutrition and Epidemiology at the Wageningen University. One research project was on body composition in frail elderly and the other on selection bias in a case-control study to meat consumption and colon polyps. Further she spent a 4 months training period at the Rowett Research Institute in Aberdeen, United Kingdom and a 3 months training period at the regional health service (GGD) West-Utrecht. In September 1999 she obtained her M.Sc. degree with majors in human nutrition and in epidemiology. After a working period of almost 3 months as a junior epidemiologist at a regional health service (GGD Brabant-Noordoost), she started in January 2000 as a researcher and project coordinator of the MRISC study at the department of Medical Oncology of the Erasmus MC in Rotterdam. She performed research on breast cancer screening in women with a familial or genetic predisposition, supported by the Dutch Health Insurance Council. From January 2005 she continued her research in the field of hereditary breast cancer at the department of Medical Oncology, Erasmus MC Rotterdam and is involved in a research project on primary prevention, surveillance and systematic treatment in women with (a risk for) hereditary breast cancer, supported by the Dutch Cancer Society.

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