EFFECTS AND COSTS OF BREAST CANCER SCREENING IN WOMEN WITH A FAMILIAL OR GENETIC PREDISPOSITION

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Effecten en kosten van borstkankerscreening bij vrouwen met een familiaire of genetische predispositie

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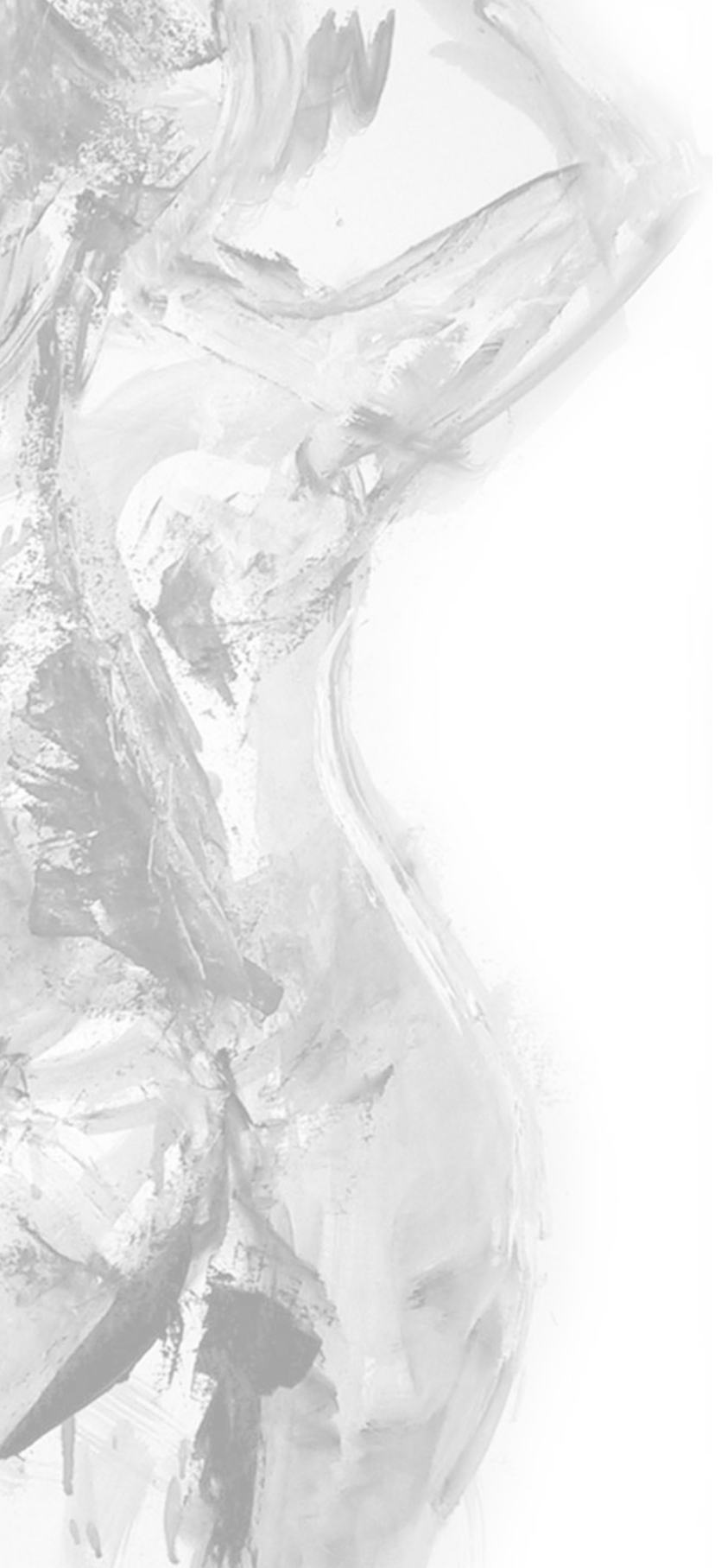

Introduction

1

BREAST CANCER INCIDENCE AND MORTALITY

Breast cancer is the most frequent type of cancer among women worldwide. Incidence rates vary around the world, with high rates in more developed countries and low but increasing rates in less developed countries. In most Western countries the average lifetime risk for women of developing breast cancer is 8-10%. Breast cancer is the leading cause of cancer death in women in Europe and the second in the United States (1, 2). Approximately 40% of the women who develop the disease will die within 10 years (3, 4).

Various factors are associated with breast cancer risk (5-7). Age is the single most important risk factor. Incidence rates increase progressively with advancing age: the steepest increase is around the menopause and the increase slows in the postmenopausal period (8). Reproductive factors like early menarche, late menopause, nulliparity and advanced age at first live birth increase the risk of developing breast cancer. Women diagnosed with benign breast disease characterized as atypical hyperplasia, also have a higher breast cancer risk. Other established risk-increasing factors are dense breast tissue on mammography, use of hormone replacement therapy, exposure to moderate-to-high levels of ionising radiation and obesity. No consensus exists whether use of hormonal contraceptives is a risk factor for breast cancer development (9, 10). Protective factors for breast cancer include breast-feeding (11), intake of folate (12) and carotenoids (13), and physical activity (14).

Although environmental and lifestyle factors account for most cases of breast cancer, a genetic predisposition is suspected in approximately 5-10% of all breast cancer cases (15, 16). In the Netherlands, approximately 25% of these cases may be attributed to the *BRCA1* and *BRCA2* breast cancer susceptibility gene mutations (17). Carriers of a germ-line mutation of one of these genes have a significantly increased cumulative lifetime risk of developing breast cancer, varying from 50 to 85% (18). Other breast cancer susceptibility genes may also play a role, but either they have not yet been identified or their role is still not clear (19). Women from families with a clear family history of breast cancer where a mutation has not (yet) been found are also at increased risk, which has mainly been estimated using the risk tables of Claus et al. (20).

In the Netherlands, the number of women with a familial or genetic predisposition to breast cancer is estimated to be 2.5% of the total female population (21), with 0.35% being *BRCA1/2* mutation carriers (22). Consequently, estimated prevalence in the Netherlands in 2004 is 23,000 *BRCA1/2* mutation carriers and 140,000 women with a strong family history, in women aged 0-60 years (for comparison: Dutch female population aged 0-60 years is 6,506,000 (23)). Estimated incidence of hereditary breast cancer in the Netherlands is 650-1275 cases per year (year 2002) (15, 16, 24, 25), and estimated total number of hereditary breast cancer deaths in the Netherlands is 175-350 per year (year 2002) (15, 16, 26).

For women with average breast cancer risk, there are several options to reduce the risk of breast cancer death, such as primary prevention (e.g. life style changes), early detection by screening or effective treatment. With screening, diagnosis will shift towards earlier stages of cancer, and further development of the disease and subsequent cancer-related death may be prevented, assuming that earlier treatment leads to better prognosis. For *BRCA1/2* mutation carriers and women with a strong family history, the risk of breast cancer can be reduced by

prophylactic mastectomy (27, 28), prophylactic oophorectomy (29, 30) or chemoprevention (31). Early diagnosis as a result of intensive screening may be an alternative risk-reducing strategy, but it is unknown whether screening decreases the rate of death from breast cancer in women with increased breast cancer risk.

MAMMOGRAPHY SCREENING FOR BREAST CANCER

Randomised controlled trials in the general population have shown that breast cancer screening by mammography can reduce mortality from the disease. An updated overview of four Swedish randomised trials showed a breast cancer mortality reduction in invited women of 16% (50-59 years) and 33% (60-69 years) respectively (32). Also in service mammography screening programmes a reduction in breast cancer mortality rates is seen (33).

However, there is no consensus about the value of breast cancer screening among women aged 40-49 years. Combining all population based randomised controlled trials showed a significant breast cancer mortality reduction in this age group, but most of this reduction might be attributable to screening these women after they reach age 50 (34, 35). Moreover, mammographic visibility of breast tumours is lower in women under 50 years. The main reason is that pre-menopausal women have denser breasts, making it more difficult to detect tumours than in post-menopausal women (36, 37). Also a higher tumour growth rate in pre-menopausal women compared to post-menopausal women is seen (38). No data from randomised trials on breast cancer screening are available for women under age 40.

Women with increased risk for breast cancer due to a familial or genetic predisposition are often diagnosed before the age of 50 years (39, 40). Guidelines for screening these women mostly consist of biannual clinical breast examination (CBE) and annual mammography, and instructions for monthly breast self-examination (BSE) (41). These recommendations are based on expert opinion: because of ethical reasons, there has been no randomised controlled trial demonstrating its effectiveness in terms of breast cancer mortality reduction. A limited number of observational studies describe the preliminary results of screening by mammography and CBE in women with increased breast cancer risk: the sensitivity of mammography screening was low (especially in *BRCA1/2* mutation carriers), which was mainly caused by the relatively young age (pre-menopausal) of these women (42-45).

In the Netherlands, eight specialized familial-cancer clinics offer intensive surveillance to women with increased risk for breast cancer due to a familial or genetic predisposition. Until recently, these women were screened according to the generally applied guidelines (biannual CBE and annual mammography) (41). Estimated number of women attending these clinics is 2000-2500 per year. This number will probably rise in the near future: a recent Dutch study estimated that, according to current national referral criteria, 25% of the first-degree relatives of a breast cancer patient should be referred for regular surveillance in a family cancer clinic (21).

MRI SCREENING FOR BREAST CANCER IN WOMEN WITH A FAMILIAL OR GENETIC PREDISPOSITION

Contrast-enhanced magnetic resonance imaging (MRI) of the breast has been shown to have high sensitivity in a diagnostic setting (46, 47), and it is less affected by breast density (48). This screening modality might improve the sensitivity of screening in younger, pre-menopausal ages, which is most important in women with a familial or genetic predisposition to breast cancer. Several countries, including the Netherlands, have started large prospective MRI screening studies, investigating the effectiveness of MRI screening in these women (49-52).

The Dutch MRI screening study (MRISC study) started November 1999 and was activated at six (out of eight) familial-cancer clinics (two cancer centres and four university hospitals). The aims were to investigate:

- The value of regular screening in women at high risk for breast cancer due to a familial or genetic predisposition
- The efficacy of MRI compared to mammography for screening in these women
- The long-term effectiveness (in terms of breast cancer mortality reduction) and cost-effectiveness of alternative screening policies
- The impact of the screening process on health-related quality of life and psychological distress

Women with >15% cumulative lifetime risk for breast cancer, who were already under regular surveillance or who came for the first time to a family cancer clinic, were asked to participate in the MRISC study. Women with evident symptoms suspicious for breast cancer or with previous breast cancer were excluded. Participants were screened twice a year, with biannual CBE and annual mammography and MRI. All women got instructions for monthly BSE.

First results of the study, with a median follow-up period of 2.9 years of 1952 included women, showed that intensive screening including MRI can detect breast cancer at an early stage in women with an inherited susceptibility to breast cancer. MRI appeared to be more sensitive than mammography in detecting invasive tumours in these women (79.5% vs. 33.3%), but both the specificity and positive predictive value of MRI were lower. The study also showed that mammography had a higher sensitivity than MRI for detecting ductal carcinoma in situ in these women (53, 54). Meanwhile, two other studies carried out in the UK and Canada also demonstrated that MRI is more sensitive for detecting breast cancers than mammography in *BRCA1/2* mutation carriers and women with a strong familial history (55-58).

However, long-term effectiveness in terms of breast cancer mortality reduction of screening women with increased breast cancer risk is still unknown, and would need substantial study follow-up. Also the cost-effectiveness of mammography and MRI screening in these women is unknown. Costs of MRI are relatively high, and more follow-up imaging and benign biopsies will be performed because of lower specificity of MRI compared to mammography (53-58). Costs of mammography are relatively low, but so is sensitivity. Therefore a well-validated breast cancer-screening model, successfully applied in the evaluation of different cancer-screening programmes (33, 34, 59), was used to predict effectiveness and cost-effectiveness of different screening policies for these women.

Besides MRI, there may be a potential role of ultrasonography in screening women with

increased breast cancer risk. Trials are underway to assess the value of ultrasonography for women at high risk (60). In studies that supplemented mammography with both MRI and ultrasonography, MRI had higher sensitivity and specificity than ultrasonography (57, 61, 62). However, the cost of ultrasonography will be lower compared to MRI.

BREAST CANCER SCREENING IN WOMEN WITH A FAMILIAL OR GENETIC PREDISPOSITION: EFFECTS ON HEALTH-RELATED QUALITY OF LIFE AND PSYCHOLOGICAL DISTRESS

Any method of breast-cancer screening has the potential for benefit and for harm. For example, the screening process itself may cause unfavourable side effects on health-related quality of life, like pain, discomfort and feelings of anxiety and distress. Several studies have shown that women with normal results after mammography screening experience no important negative psychological consequences, whereas recall because of a false-positive mammogram causes adverse emotional, physical and social effects (63-66).

Intensive screening in women at high risk for breast cancer due to a familial or genetic predisposition is increasing, while its long-term effectiveness is still unknown. It is therefore important to pay attention to possible unfavourable side effects on health-related quality of life and distress, which may arise from the screening process. Only one study reported that screening appeared to be less stressful for women with a family history than for those without (66). Lodder et al (67) showed that women opting for prophylactic mastectomy had significant higher distress levels than mutation carriers who opted for surveillance. However, no studies have been performed to investigate the short-term effects of intensive screening on health-related quality of life in women with increased breast cancer risk. Also the acceptance of MRI screening in these women is unknown.

COST-EFFECTIVENESS ANALYSIS IN SCREENING

In a cost-effectiveness analysis, a trade-off is made between cost and effects of health care interventions (68). Effects are health outcomes, for screening usually expressed in terms of deaths prevented, life-years gained or quality-adjusted life-years gained. Effectiveness of different screening policies can be compared. From a public health perspective, it is also important to consider the costs in comparing different screening strategies. Costs of a screening strategy consist of extra costs of screening, diagnostics and treatment. Cost-effectiveness ratios, expressed as cost per life-year gained, and incremental cost-effectiveness ratios, expressed as additional cost per additional life-year gained, can be calculated. The incremental cost-effectiveness ratio of a screening strategy compared to a less intensive screening strategy is the ratio between the extra costs of the intensive strategy and the extra life-years gained by the intensive screening strategy. In order to calculate costs and effects of alternative screening policies that have not been studied in observational studies, a model-based approach can be used, extrapolating the results of randomised controlled trials and observational studies.

THIS THESIS

Research questions

The objective of this thesis was to investigate important questions in screening women at high risk for breast cancer due to a familial or genetic predisposition. Although first results of the MRISC study showed that intensive screening including MRI can detect breast cancer at an early stage in these women, other important issues concerning screening these women were still unknown.

The main questions in this thesis to be addressed are:

1. What are the quality of life and psychological effects of the screening process in screening women with a familial or genetic predisposition to breast cancer?
2. What are the breast cancer mortality effects and cost-effectiveness of various screening policies, including MRI, for women with a familial or genetic predisposition to breast cancer?

Structure of the thesis

Part I of the thesis addresses the first research question. Chapter 2 describes the development and testing of the Dutch Psychological Consequences Questionnaire (PCQ), by assessing the acceptability, internal consistency, scale structure and validity of the questionnaire. In the MRISC study, the PCQ was used to measure the psychological impact of breast cancer screening in women with a familial or genetic predisposition.

Chapter 3 evaluates the role of (cognitive and affective) risk perception in the psychological burden of breast cancer screening in women with a familial or genetic predisposition.

Chapter 4 describes the short-term effects of screening for breast cancer on generic health-related quality of life and distress, in women with a familial or genetic predisposition.

Chapter 5 examines the association between psychological distress and reported breast self- examination frequency in women with increased breast cancer risk who are screened regularly.

Since MRI is a relatively new screening modality in breast cancer management, the acceptance of MRI screening is explored in chapter 6.

Part II of the thesis addresses the second research question. The main objective of this part is to predict the effectiveness and cost-effectiveness of alternative screening policies for women with a familial or genetic predisposition to breast cancer, with MRI, mammography and CBE as possible screening modalities. Since no randomised controlled trial of CBE compared to no screening has been completed (69), the Canadian National Breast Screening Study-2 (CNBSS-2) is used to estimate stage-specific CBE sensitivities.

In chapter 7 a modelling effort of the CNBSS-2 is conducted. The CNBSS-2 was a randomised controlled trial designed to evaluate the efficacy of annual mammography over and above annual CBE. Because the control arm was screened, no estimations of mammography benefit compared to no screening could be made, as is available from other mammography trials, nor any estimate of the benefit of CBE screening. The model evaluation of the CNBSS-2 results in estimates of the benefit of mammography or CBE compared to no screening in terms of breast cancer mortality reduction, and in estimates of stage-specific sensitivities of both

screening modalities.

Since the usefulness of CBE as a screening modality is uncertain, chapter 8 explores the effectiveness and cost-effectiveness of CBE screening when implemented in the Dutch nation-wide screening programme, as well as the usefulness of adding CBE to mammography screening. Estimated stage-specific sensitivities of CBE, resulting from the model evaluation of the CNBSS-2, are used.

Chapter 9 predicts the effectiveness and cost-effectiveness of alternative screening policies for women with a familial or genetic predisposition to breast cancer. Here also estimated stage-specific sensitivities of CBE, resulting from the model evaluation of the CNBSS-2, are used.

Lastly, in chapter 10, a summary of the results is given and the two research questions are answered. Additional aspects of screening women with a familial or genetic predisposition to breast cancer are discussed, and suggestions for future research are given.

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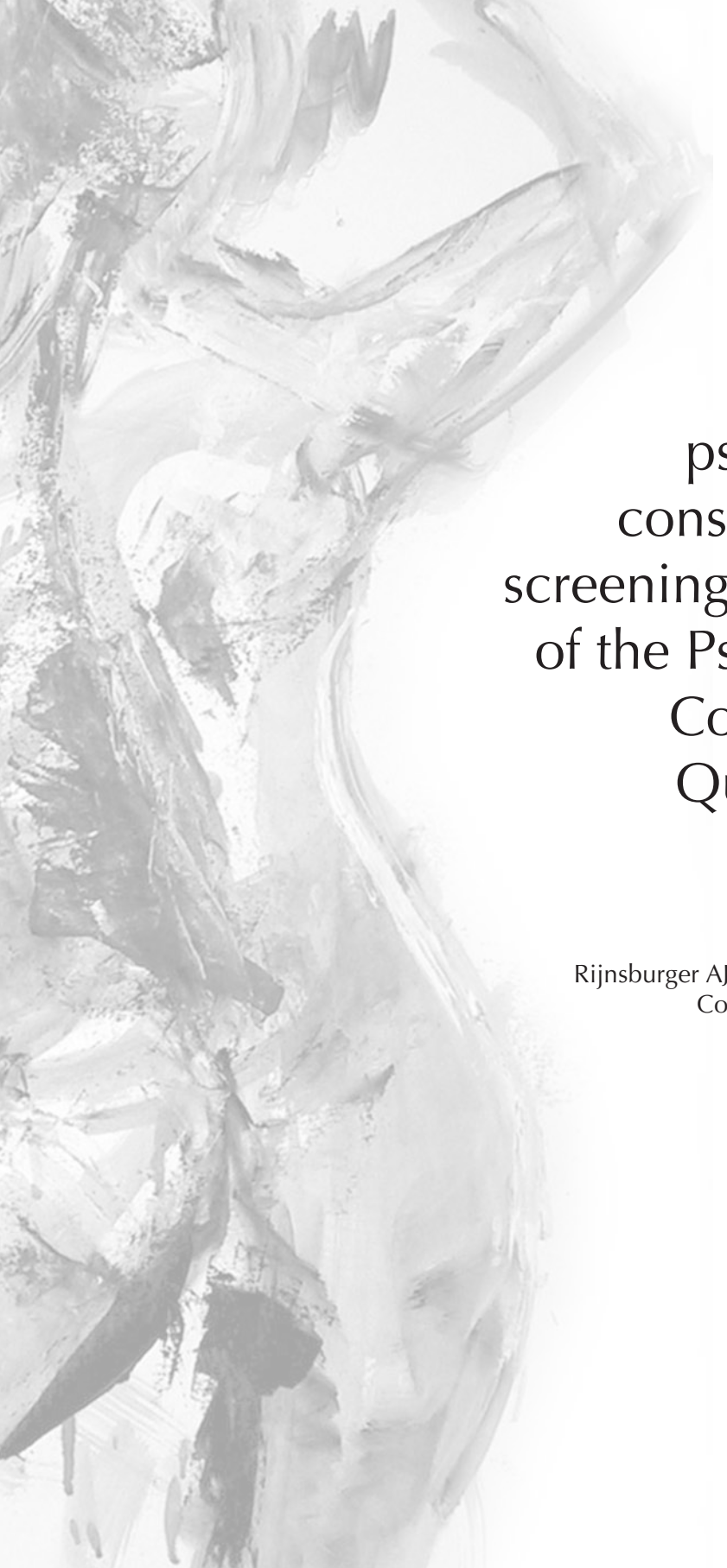
PART I

SCREENING WOMEN WITH A FAMILIAL OR GENETIC PREDISPOSITION TO BREAST CANCER: QUALITY OF LIFE AND PSYCHOLOGICAL EFFECTS OF THE SCREENING PROCESS



Measuring psychological consequences of screening: adaptation of the Psychological Consequences Questionnaire into Dutch

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Submitted

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ABSTRACT

Objective – To assess the psychometric properties of a Dutch adaptation of an originally Australian instrument measuring the psychological impact of breast cancer screening.
Methods – The three subscales (emotional, physical, social) of the Psychological Consequences Questionnaire (PCQ) underwent formal linguistic and cultural translation. A total of 524 women under intensive surveillance because of increased breast cancer risk were asked to complete the questionnaire at 2 months prior to screening, at the day of the screening visit preceding the screening, and 1 to 4 weeks after screening. Acceptability, score distribution, internal consistency, scale structure, responsiveness to change and construct validity were analysed.
Results – Response rates were high (98%-94%) and there were very few missing answers and non-unique answers. All scales had Cronbach's alphas > 0.70. The physical and social subscale showed ceiling effects. The item-own scale correlations were only slightly higher than the corresponding item-other scale correlations. Factor analysis showed that the assumed three separate subscales were replicated in our study. Pre- and post-screening effect sizes for the emotional scale were larger than for the other two scales. All PCQ scales correlated with the scales of two other psychological measures ($P \leq 0.01$). The emotional scale and the total PCQ score were able to differentiate between subgroups varying in affective risk perception ($P \leq 0.01$).
Conclusions – The Dutch PCQ is useful in measuring psychological impact among women under intensive surveillance because of high breast cancer risk.

Acknowledgements
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INTRODUCTION

Intensive surveillance in women at high risk for breast cancer due to a familial or genetic predisposition is increasing, although its effectiveness in terms of breast cancer mortality reduction is yet unknown. Prospective studies, like the ongoing MRI screening study (MRISC study) in the Netherlands, now have shown that intensive surveillance including magnetic resonance imaging (MRI) can detect breast cancer at an earlier stage in these women (1, 2). Because unfavourable side effects on psychological well-being and health-related quality of life may arise from the process of screening itself, we conducted an empirical psychological follow-up study and health-related quality of life study alongside the MRISC study (3).

To measure the psychological impact of breast cancer screening in high-risk women, we chose to use the Psychological Consequences Questionnaire (PCQ), developed to measure the effects of breast screening on emotional, physical and social functioning (4). The PCQ was successfully used in different studies measuring psychological morbidity related to mammography screening (5-10), and was found to be an adequate questionnaire for measuring short-term consequences of false-positive screening (11). Consistent with use in the literature (5-7, 9, 10), we adapted the three subscales into Dutch (Table 1). Five items measure emotional dysfunction, four measure physical dysfunction, and three measure social dysfunction. Ratings for symptoms within each dimension vary from 0 (not at all) to 3 (quite a lot of time), and are added to give a score indicating the level of dysfunction on that dimension. Because Ong et al. (6) found that the three subscales were highly correlated and measured the same single

Table 1. Items and layout of the Psychological Consequences Questionnaire (PCQ)*

Subscale†	Over the last week how often have you experienced the following because of thoughts and feelings about breast cancer:	Not at all	Rarely	Some of the time	Quite a lot of the time
P	Had trouble sleeping	0	1	2	3
P	Experienced a change in appetite	0	1	2	3
E	Been unhappy or depressed	0	1	2	3
E	Been scared and panicky	0	1	2	3
E	Felt nervous or strung up	0	1	2	3
E	Felt under strain	0	1	2	3
S	Found you have been keeping things from those who are close to you	0	1	2	3
S	Found yourself taking things out on other people	0	1	2	3
S	Found yourself noticeably withdrawing from those who are close to you	0	1	2	3
P	Had difficulty doing things around the house which you normally do	0	1	2	3
P	Had difficulty meeting work or other commitments	0	1	2	3
E	Felt worried about your future	0	1	2	3

* The Dutch version of the PCQ is available on request from the authors.
† Letters indicate the three subscales: E = emotional; P = physical; S = social.

concept of adverse psychological consequences, we also used one overall total PCQ score in which the scores of all items were added up.

This brief communication describes the development and testing of the Dutch PCQ, by assessing the acceptability, internal consistency, scale structure and validity of the questionnaire in a population of women under intensive surveillance because of high risk for breast cancer. The PCQ has not been used in this setting before.

MATERIAL AND METHODS

Dutch version of the PCQ

Independent forward and backward translation procedures were applied for the PCQ scales (12). The instrument was qualitatively pilot tested in 10 women under intensive surveillance because of high breast cancer risk.

Study population and data collection

The MRISC study is a prospective cohort study designed to assess the efficacy of mammographic and MRI screening in high-risk women (1, 13). Participants in the MRISC study were approached for the psychological follow-up study. Women completed questionnaires 2 months prior to the scheduled screening visit (baseline, T0), at the day of the scheduled screening visit, preceding the screening (T1), and 1 to 4 weeks after screening (T2) for women without breast cancer. Women with a screen-detected or interval breast cancer did not receive any questionnaire after the diagnosis. The design of this study is described in more detail elsewhere (3).

Questionnaires with at least an 80% response to PCQ-items were eligible for analysis. In case of a missing answer in eligible questionnaires, median scores per item were imputed, because PCQ scales were highly skewed. In case of non-unique answers (more than one answer per question), one answer was imputed randomly.

Analyses

Acceptability:

We evaluated acceptability by assessing the response rates and the percentage of missing / non-unique answers per item at the three data collection points, and by remarks of respondents (50 randomly selected T0 questionnaires).

Internal consistency:

Cronbach's alpha was used to evaluate the internal consistency of the PCQ scales at T1 (14). We assessed whether correlations (Pearson's product moment coefficients) between items and their own scale score (without the item under consideration) were higher than the correlations between these items and any other scale.

Scale structure:

To determine whether the items were well chosen and if scales represent separate entities, we performed factor analysis (principal component analysis with Varimax rotation), which identi-

fies separate factors within the instrument (15).

Responsiveness:
We expected an increase in emotional dysfunction from T0 to T1, and a decrease in emotional dysfunction from T1 to T2. Responsiveness to these changes was measured with an effect size statistic: d = [Mean (second measurement) – Mean (first measurement)] / SD at the first measurement (16), with $0.2 \leq |d| < 0.5$ indicating a small effect size, $0.5 \leq |d| < 0.8$ a moderate effect size, and $|d| \geq 0.8$ a large effect size (17).

Construct validity:
Spearman's rank order correlation coefficients were applied to evaluate the construct validity of the PCQ scales with two psychological measures at T1: the Hospital Anxiety and Depression Scale (HADS) (18), a generic psychological instrument, and the Impact of Event Scale (IES) (19), an event specific psychological instrument which can be tailored to a specific event, namely 'breast cancer' in this study.

Affective risk perception was assessed by asking women how they feel about their chance of developing breast cancer, with answer categories on a 7-point Likert scale with labelled end points "very low" and "very high" (20). The responses were subsequently trichotomised for analysis into "quite to very low", "not low and not high" and "quite to very high". The discriminative ability between these subgroups at T1 was assessed by Kruskal-Wallis tests, and by effect sizes defined as d = [Mean (subgroup b) – Mean (subgroup a)] / highest SD of both subgroups, resulting in relatively conservative effect size estimates.

To evaluate internal consistency, scale structure and construct validity, data of the PCQ scales at T1 were used, because we expected most variation in dysfunction at that specific moment in the screening process.

RESULTS

Response rates and sample characteristics

From September 2000 to June 2003, 524 women were approached for the psychological follow-up study. A baseline (T0) questionnaire was sent to 358 women; the remaining women declined to participate (n=110), did not respond to the participation request (n=49) or dropped out before sending a T0 questionnaire (n=7). At time of analyses we had 348 (T0), 342 (T1) and 332 (T2) completed and evaluable questionnaires.

Response rates were high among those who consented to participate (T0: 98%; T1: 96%; T2: 94%). The mean age of participants at T0 was 41.1 years (SD = 8.9) and they had spent an average of 5.3 years (SD = 4.4) under regular surveillance.

Acceptability

Hardly any questionnaire had less than 80% response to PCQ-items (T0: 1; T1: 2; T2: 1). The PCQ showed very few missing answers (0.33-0.61% per item on average) and non-unique answers (0-0.05% per item on average) at the three data collection points. No specific remarks

Table 2. Score-distribution and psychometric properties of the Dutch Psychological Consequences Questionnaire (PCQ) scales at T1 (day of screening; n = 340)

Scales	No. of items	Mean (SD)	Observed range	Min* (%)	Max† (%)	25th percentile	50th percentile	75th percentile	Cronbach's α‡	Average inter-item correlation	Average item-own scale correlation	Average item-other scale correlation
Emotional dysfunction (theoretical range 0-15)	5	3.0 (3.4)	0-15	31.8	1.2	0.0	2.0	5.0	0.90	0.66	0.76	0.61
Physical dysfunction (theoretical range 0-12)	4	1.1 (1.9)	0-11	59.1	0.0	0.0	0.0	2.0	0.74	0.43	0.55	0.53
Social dysfunction (theoretical range 0-9)	3	1.1 (1.8)	0-8	56.5	0.0	0.0	0.0	1.0	0.78	0.54	0.63	0.59
Total PCQ score (theoretical range 0-36)	12	5.3 (6.4)	0-32	28.5	0.0	0.0	3.0	8.0	0.92	0.50	0.68	

* Percentage of respondents with best possible score.
† Percentage of respondents with worst possible score.
‡ Average α-value of the three scales is 0.81.

regarding the PCQ were made by the respondents, suggesting a good understanding and general acceptance of the questionnaire.

Score distribution

Mean PCQ scale scores were low and showed highly skewed distributions (Table 2). The physical and social scale showed ceiling effects: a considerable (> 50%) percentage of the women had the best possible score, which indicated no dysfunction.

Internal consistency

All scales had a Cronbach's alpha > 0.70 (Table 2). The item-own scale correlations of the PCQ scales were only slightly higher than the corresponding item-other scale correlations.

Scale structure

Factor analysis showed that for the emotional and physical subscale, all of its items loaded on the same factor (Table 3). Only for the social subscale, all but one of its items ("Found yourself taking things out on other people") loaded on the same factor.

Responsiveness to change

Pre-screening effect sizes were moderate for the emotional scale and the total PCQ score (Table 4). Post-screening effect sizes were small, but for the emotional scale it was higher than for the other two scales.

Table 3. Factor loadings (after Varimax rotation) of the Dutch Psychological Consequences Questionnaire (PCQ) scales at T1 (day of screening; n = 340)

Subscale*	Over the last week how often have you experienced the following because of thoughts and feelings about breast cancer:	Factor		
		1	2	3
E	Been unhappy or depressed	**0.575**	0.540	0.324
E	Been scared and panicky	**0.724**	0.279	0.273
E	Felt nervous or strung up	**0.768**	0.489	0.085
E	Felt under strain	**0.693**	0.531	0.135
E	Felt worried about your future	**0.792**	0.107	0.443
P	Had trouble sleeping	0.164	**0.618**	0.210
P	Experienced a change in appetite	0.274	**0.526**	0.131
P	Had difficulty doing things around the house which you normally do	0.230	**0.672**	0.318
P	Had difficulty meeting work or other commitments	0.331	**0.679**	0.179
S	Found you have been keeping things from those who are close to you	0.268	0.291	**0.826**
S	Found yourself taking things out on other people	0.218	**0.623**	0.266
S	Found yourself noticeably withdrawing from those who are close to you	0.289	0.467	**0.714**

* Letters indicate the original three subscales: E = emotional; P = physical; S = social.

Table 4. Effect sizes (*d*) from T0 (2 months prior to screening) to T1 (day of screening) and from T1 (day of screening) to T2 (1 to 4 weeks after screening, with message 'no breast cancer')*

Scales	T0 vs. T1 (n = 332)	T1 vs. T2 (n = 320)
Emotional dysfunction	0.60	-0.45
Physical dysfunction	0.42	-0.32
Social dysfunction	0.28	-0.33
Total PCQ score	0.50	-0.42

* Interpretation: $0.2 \leq |d| < 0.5$ = small effect; $0.5 \leq |d| < 0.8$ = moderate effect; $|d| \geq 0.8$ = large effect.

Table 5. Construct validity of the Psychological Consequences Questionnaire (PCQ) assessed by Spearman correlation between the PCQ scales and Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale (IES) domains respectively, at T1 (day of screening; n = 340)

PCQ	Emotional dysfunction	Physical dysfunction	Social dysfunction	Total PCQ score
HADS				
Anxiety	0.61*	0.50*	0.50*	0.62*
Depression	0.43*	0.36*	0.40*	0.44*
IES				
Intrusion	0.70*	0.51*	0.56*	0.70*
Avoidance	0.63*	0.50*	0.52*	0.64*

* $P \leq 0.01$ level (2-tailed)

Construct validity

All PCQ scales showed larger correlations with the anxiety scale of the HADS than with the depression scale, although all correlations were significant at the 0.01 level (Table 5). The PCQ scales also correlated with the intrusion and avoidance scale of the IES ($P \leq 0.01$ for all values).

As shown in Table 6, the emotional scale of the PCQ and the total PCQ score were able to differentiate between subgroups varying in affective risk perception ($P \leq 0.01$). The emotional scale discriminated well between a subgroup of women with "quite to very low" risk perception and those with "quite to very high" risk perception ($d = 0.54$). This was at least equivalent to the discriminative ability of the HADS and the IES in this study.

DISCUSSION

Our study results report a good performance of the Dutch PCQ in terms of acceptability, internal consistency, scale structure and construct validity. Response rates were high and there were few missing answers and non-unique answers. All scales had sufficient Cronbach's alphas, which were comparable with the results from other studies (4, 8, 9). However, the

Table 6. Discriminative ability of the Psychological Consequences Questionnaire (PCQ), Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale (IES) between groups differing in affective risk perception, at T1 (day of screening; n = 331*)

	Affective risk perception			P-value†	Effect size (*d*) "quite to very low" vs. "not low and not high"‡§	Effect size (*d*) "quite to very low" vs. "quite to very high"‡§
	Quite to very low n = 41 mean (SD)	Not low and not high n = 98 mean (SD)	Quite to very high n = 192 mean (SD)			
PCQ						
Emotional dysfunction	1.6 (2.3)	2.4 (3.0)	3.5 (3.5)	≤ 0.01	0.24	0.54
Physical dysfunction	0.7 (1.5)	0.9 (1.8)	1.2 (2.0)	0.08	0.11	0.26
Social dysfunction	0.8 (1.2)	0.9 (1.7)	1.3 (1.9)	0.10	0.08	0.25
Total PCQ score	3.1 (4.6)	4.2 (5.7)	6.0 (6.7)	≤ 0.01	0.18	0.43
HADS						
Anxiety	3.8 (3.5)	5.6 (4.0)	5.5 (3.8)	≤ 0.01	0.45	0.46
Depression	1.6 (2.2)	2.6 (3.2)	2.7 (3.1)	0.14	0.32	0.35
IES						
Intrusion	2.5 (3.7)	4.0 (5.8)	5.9 (6.6)	≤ 0.01	0.26	0.53
Avoidance	3.6 (5.6)	4.0 (7.3)	5.2 (6.5)	≤ 0.05	0.05	0.24

* 9 women had missing data for affective risk perception.
† Two-sided Kruskal-Wallis test given a non-normal distribution of the data.
‡ Difference of the means divided by the highest SD of both subgroups.
§ Interpretation: $0.2 \leq |d| < 0.5$ = small effect; $0.5 \leq |d| < 0.8$ = moderate effect; $|d| \geq 0.8$ = large effect.

physical and social subscale showed profound ceiling effects. This limits the use of these scales when attempting to detect changes in women at high risk for breast cancer who have no or very limited dysfunction.

As expected, pre- and post-screening effect sizes for the emotional scale were larger than for the other two scales, and were small to moderate. This shows the instrument's responsiveness. Also, as expected, the ability to discriminate between subgroups varying in affective risk perception was better for the emotional subscale than for the other two subscales.

The performance of the PCQ in this study was at least equivalent to that of the HADS and the IES: direct comparison of the PCQ scales with the HADS (especially with the anxiety domain) and IES domains supported the validity of the scales. As the IES (tailored to the specific event 'breast cancer') and the PCQ appear to be measuring similar concepts, using both measures in a study of women at high risk for breast cancer may not be warranted.

For the social subscale, one item ("Found yourself taking things out on other people") did not load on the original factor. We considered translation errors as possible cause, but after renewed independent forward and backward translation procedures this did not seem to be the problem.

The item-own scale correlations of the PCQ scales were only slightly higher than the item-other scale correlations, indicating that the three subscales partly overlap. Ong et al. (6) found that many items of the PCQ correlated lower with their own subscale than with the other two identified subscales, which is even stronger than the results from our study. However, factor analysis showed that the original groupings of items (scales) were almost completely replicated in our study. Therefore, the use of the three subscales is advised, although the additional use of one overall total PCQ score may be considered. In our study the total PCQ score showed good responsiveness and construct validity, comparable to the emotional subscale.

We conclude that the PCQ has been translated successfully into Dutch, and that the Dutch PCQ is useful in measuring psychological impact among women under intensive surveillance because of high breast cancer risk.

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Psychological distress in women at increased risk for breast cancer: the role of risk perception

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ABSTRACT

Background – The magnetic resonance imaging screening (MRISC) study evaluates a surveillance programme for women with a hereditary risk for breast cancer. The psychological burden of surveillance in these women may depend on inaccurate risk perceptions. We examined differences in risk perception between three predefined risk categories and associations with psychological distress.
Methods – Breast cancer-specific distress, general distress, and risk perception (cognitive and affective) were assessed, two months before a surveillance appointment. Cumulative lifetime risk (CLTR) of developing breast cancer was trichotomised into: (1) CLTR of 60-85% (mutation carriers), (2) CLTR of 30-50%, and (3) CLTR of 15-30%.
Results – In a total group of 351 women (mean age 40.5 years, range 21-63 years) the three risk categories significantly differed in their accuracy of assessing cognitive risk perception. In category 1, 60% had an accurate risk perception, in category 2, 43.7% and in category 3, 33.3%. Overestimators reported significantly more breast cancer-specific distress. After adding affective risk perception to the model, this effect disappeared. Affective risk perception showed significant associations with breast cancer-specific and general distress.
Conclusions – Affective risk perception is a more important determinant for psychological distress than cognitive risk perception. This knowledge should be used during surveillance appointments in order to improve and individualise support for these women.

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INTRODUCTION

One in every ten women in Western industrialised countries will develop breast cancer during her life-time. A genetic predisposition is suspected in approximately 5-10% of all breast cancer cases. In the mid-1990s, the *BRCA1* and *BRCA2* genes were identified (1, 2). Carriers of a mutation in one of these genes have a significantly increased cumulative lifetime risk (CLTR) of developing breast cancer that has been reported to be between 60% and 85% (3-5), while Antoniou and colleagues (6) recently provided evidence for lower risk percentages in breast cancer patients unselected for family history. Other breast cancer susceptibility genes may also play a role, such as CHEK2 (7), but either their role still has to be elucidated or such genes are not yet identified. Women from families with a clear family history of breast cancer where a mutation has not (yet) been found are also at increased risk, which has mainly been estimated using the risk tables developed by Claus and colleagues (8). Since the Claus model does not account for bilateral breast cancer, the occurrence of breast cancer in multiple family members as well as the occurrence of ovarian cancer, other models are also being developed, and may eventually provide more accurate risk estimations (9). One of the management options for women at increased risk is regular surveillance mostly by use of an annual mammography and biannual clinical breast examination. A monthly breast self-examination is recommended.

Perceptions of the risk of developing breast cancer in 'high-risk' women are frequently found to be inaccurate, but also show a wide variability. In the literature, between 9% and 57% of 'high-risk' women are reported to have accurate risk perceptions (10-16). This variability can partly be explained by which the risk perception is measured, either before or after counselling. Meiser and colleagues conducted a meta-analytical review in order to obtain an effect size of the impact of genetic counselling on the accuracy of risk perception. They found a significant medium effect size ($r = 0.56$; $P < 0.01$) which demonstrates the efficacy of genetic counselling in improving risk perception (17). Despite improvements in accurate risk perception after genetic counselling, there are still women who continue to overestimate or underestimate their breast cancer risk (10, 12, 14, 18-21). Several reasons for sustained inaccurate risk perceptions can be given. Lacking sufficient numerical skills or overall education levels can cause inaccurate risk perceptions (22). Processing information about heredity can lead to wrong assumptions about one's risk of developing the disease, for instance on the basis of physical or psychological identification with an affected relative (23). Personal experience with breast cancer in the family may obstruct the adoption of realistic risk perceptions (24). The format in which the risk information is given may also influence the accuracy of recall of the risk estimation. Watson and colleagues found that recall of risk is more accurate when risk information is given in Odds Ratios than in other formats (12).

Women with higher risk perceptions often display more psychological distress, both breast cancer-specific and general (11, 12, 15, 16, 20, 25). Hopwood and colleagues (16) found more cancer worries in overestimators than in women who underestimated or who estimated their risk accurately. Meiser and colleagues (15) found that overestimators had both higher state anxiety, as well as breast cancer anxiety. These data result from studies that addressed the level of knowledge of risk, i.e., the cognitive dimension. Women had to indicate how they *think* about their own risk by ticking a number. Hopwood suggested that not only the objec-

tive risk information may be of importance, but also the way this information is processed by the individual (13). This led us to hypothesise that, women may give an accurate or inaccurate estimation of their breast cancer risk, but the way they feel about this risk may be very much lower or higher. Further, this felt or affective risk perception may have a more powerful association with psychological distress than cognitive risk perception.

In November 1999, the observational magnetic resonance imaging screening (MRISC) study started in the Netherlands evaluating a surveillance programme for women at increased risk of breast cancer due to a genetic or familial predisposition (MRISC-part A). The programme consisted of an annual magnetic resonance imaging (MRI) scan and mammography, biannual physical examination and monthly breast self-examination. The participants were classified into one of three risk categories, corresponding to a CLTR of either more than 60%, a CLTR of 30-50%, and a CLTR of 15-30% (26). A psychological follow-up study started in September 2000 (MRISC-part B). Here, we describe the association between psychological distress and risk perception in women participating in the MRISC-part B. First, we differentiated between a cognitive and an affective component of risk perception in the three different levels of objective risk status. Next, we determined the association between general and breast cancer-specific distress, and cognitive and affective risk perception. We hypothesised that the women in the different risk categories differed in the perception of their risk; in a way that higher risk perceptions were associated with elevated levels of both types of psychological distress; and that affective risk perception was more prominently associated with psychological distress than cognitive risk perception.

MATERIAL AND METHODS

Participants

A total of 351 women were included in this study; 322 women participated in the MRISC-A study and 29 women adhered to surveillance, but were not enrolled in MRISC-A. One hundred and eight women from MRISC-A did not participate in the psychological follow-up study. At entry, participants did not have a history of breast cancer, and had a cumulative lifetime risk of developing breast cancer of at least 15%, based on risk tables by Claus and colleagues (8). For this study, participants were categorised in one of three risk categories by means of a decision tree, which is an adapted form of the tables of Claus that has been developed for this study by a genetic subcommittee (26). Women in category 1 were identified *BRCA1* or *BRCA2* mutation carriers with a cumulative lifetime risk (CLTR) of developing breast cancer of between 60% and 85%. Women in category 2 had a CLTR of between 30% and 50%, and were first-degree family members of a proven *BRCA1/2* mutation carrier, who did not opt for the test themselves, or first-degree relatives from a breast cancer patient from a non-*BRCA1/2* mutation family or a family where genetic testing was not performed. Women in category 3 had a CLTR of between 15% and 30% and belonged to families with an increased frequency of breast cancer incidence, or were 25% risk carriers from a proven *BRCA1/2* mutation family (27, 28). Participants signed informed consent and had an adequate understanding of the Dutch language. The Medical Ethical Committee of the Erasmus MC in Rotterdam approved the study.

Question 1:

"How do you estimate your chance of developing breast cancer?"
My chance of developing breast cancer is:
☐ very unlikely
☐ about 1 in 20 (i.e. 5%)
☐ about 1 in 10 (i.e. 10%)
☐ about 1 in 7 (i.e. 11 – 19%)
☐ about 1 in 4 (i.e. 20 – 29%)
☐ about 1 in 3 (i.e. 30 – 39%)
☐ about 1 in 2 (i.e. 40 – 50%)
☐ greater than 1 in 2 (i.e. 60 – 80%)

Question 2:

Besides this estimated chance, you possibly have a certain feeling about your chance of developing breast cancer.
"What do you feel your chance of developing breast cancer is?"
I feel my chance of developing breast cancer is:
☐ very small
☐ small
☐ reasonably small
☐ not small, not high
☐ reasonably high
☐ high
☐ very high

Figure 1. Questions measuring risk perception

Measures

Independent variables

Age and the number of years adhering to regular surveillance were measured in years. Educational level was divided into lower, medium and higher levels. Lower levels meant primary education or lower vocational education; medium levels included lower or higher general secondary education or intermediate vocational education; higher levels included pre-university education, higher vocational education or university.

Being in a committed relationship and having children were dichotomised into yes and no. The risk categories were 1, 2 or 3 (see participants) (27, 28).

Risk perception was measured by two questions (see Figure 1). The first one measured the women's knowledge about her personal risk estimate of developing breast cancer in terms of "1 in x" in combination with percentages (cognitive). The second question assessed risk perception in terms of her feelings about her chance of developing breast cancer with answer-categories in words (affective).

Dependent variables

Intrusion and avoidance were measured using the Impact of Event Scale (IES). This questionnaire developed by Horowitz and colleagues comprises 15 items and can be tailored to a specific event, namely 'breast cancer' in this study (29). The IES measures two common re-

sponses to stressful situations: avoidance (8 items) and intrusion (7 items) and has four answer categories: not at all (0), seldom (1), sometimes (3) and often (5). Reliability analysis in this study revealed Cronbach Alpha's of 0.84 (avoidance) and 0.86 (intrusion).

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire, measuring anxiety (7 items) and depression (7 items) (30). Each subscale has a score range between 0 and 21. Reliability analysis in this study revealed Cronbach Alpha's of 0.83 for anxiety and 0.86 for depression.

Somatic impact was measured with the somatic subscale derived from the Symptom Checklist-90 (SCL-90). This 12-item list consists of physical symptoms often reported when functional problems occur. Each item can be answered with: not at all (1), a little (2), quite (3), very (4) or extremely (5), providing a score range between 12 and 60 (31). Reliability analysis in this study revealed a Cronbach Alpha of 0.81 for this subscale.

Design

The study was part of a longitudinal observational study on psychological impact and quality of life within the MRISC-study. This article concerns the first assessment at 2 months prior to the women's subsequent appointment in the clinic. The assessments took place between November 2000 and April 2003.

Procedure

Women participating in MRISC-A were sent a letter about the study along with written patient information, an informed consent form, a form on which women could indicate that they did not want to participate and a reply-paid envelope. Additionally, for women who had not received the mailed information but who were adhering to breast surveillance, the physician or oncologist of the family cancer clinic introduced the study and handed out the patient information at the scheduled control visit. After sending back the signed informed consent, women received their baseline questionnaire at home two months prior to their next surveillance appointment at the family cancer clinic, together with a reply-paid envelope. Women who did not return their questionnaire within 4 weeks were sent a reminder.

Genetic counselling

Women from identified *BRCA* mutation families were eligible for a DNA test and received extensive genetic counselling during the decision process. The identified *BRCA1/2* mutation carriers (risk category 1) were again elaborately informed about their risk of developing breast cancer and ovarian cancer at the moment of the test result. Women not choosing to proceed with genetic testing were categorised in risk category 2. All these women received a written summary of the information provided. Risk category 2 also includes women who received inconclusive DNA results after receiving extensive counselling and a written summary. These women have to face inaccurate risk estimations, although empirical evidence allows improved risk estimation models (9). The same holds for women belonging to risk category 3. As not all women in this risk category were eligible for a DNA test, a subgroup in this risk category has not received genetic counselling. However, this group of women was extensively informed about their breast cancer risk by the physician or oncologist seeing the women for surveillance at the family cancer clinic of our institution.

Statistics

The characteristics of the study sample were tested for differences between the three risk categories by the one-way analysis of variance method in case of continuous data and by the χ^2 method (Linear-by-Linear Association) in case of ordinal data. The cognitive risk perception question was trichotomised into underestimation, accurate estimation and overestimation of one's own risk. For risk category 1, the answer: *greater than 1 in 2* was considered as an accurate answer; for risk category 2, the answers: *about 1 in 2* and *about 1 in 3* were both considered as an accurate answer; and for risk category 3, the answers: about 1 in 4 and about 1 in 7 were both considered as accurate answers. Subsequently, this variable was recoded into dummy-variables. The affective risk perception question was considered as a continuous variable. An analysis of covariance (ANCOVA) was applied to explore how affective risk perception was related to cognitive risk perception for the three risk categories. Covariables were: age, number of years of adherence, educational level, having a relationship and having children.

Missing values in the dependent variables were handled as follows: for women who filled in more than 75% of the questions per subscale, a total score has been computed, corrected for the total number of questions of the subscale. For women who filled in less than 75% of the questions per subscale no total score was computed. With the dependent variables, a two-component structure was determined (details submitted elsewhere). The first component (Component I) constituted the outcome variables intrusion and avoidance. These are measures of distress as a consequence of intense experience or active avoidance of thoughts and feelings about breast cancer and, therefore, Component I can be characterised as breast cancer-specific distress. Component II is characterised by anxiety, depression and the somatic subscale of the SCL-90. Because the questions are to be answered without bearing in mind thoughts and feelings about breast cancer, this component can be considered to be an expression of general distress.

Multiple linear regression was used to determine differences between the three risk categories and cognitive and affective risk perception. Multiple linear regression was also used to determine the association between cognitive and affective risk perception and general and breast cancer-specific distress. The meaning of statistical adjustment is that the relationship between the variables of interest (i.e., independent variables) and the dependent variable may be biased, if possible confounding variables are not taken into account. For example, the relationship between risk perception and distress might be biased if age was not taken into account. In this study, we considered risk category, age, number of years of adherence, level of education, having a relationship and having children as potential confounder variables that require inclusion as covariates. As a measure of the relative importance the standardised regression coefficient was used. All statistical testing occurred at the 0.05 level of significance (two-sided). All analyses were carried out using the Statistical Package for the Social Sciences (SPSS 11).

Table 1. Demographic characteristics of the study sample

Variable	Risk category 1 (n = 40)	Risk category 2 (n = 199)	Risk category 3 (n = 112)	Total (n = 351)
Mean age (SD)	40.7 (10.3)	41.0 (8.8)	39.5 (8.3)	40.5 (8.8)
Mean number of years adhering to surveillance (SD)*	3.0 (12.4)	5.6 (4.4)	5.6 (4.7)	5.3 (4.4)
Educational level				
Lower level	6 (15%)[a]	34 (17%)	21 (19%)	61 (17%)
Middle level	23 (58%)	106 (53%)	59 (53%)	188 (54%)
Higher level	11 (28%)	59 (30%)	32 (29%)	102 (29%)
Having a partner (yes)	38 (95%)	173 (87%)	97 (87%)	308 (88%)
Having children (yes)	25 (63%)	147 (74%)	79 (71%)	251 (72%)

SD, standard deviation.
[a] Percentages indicate column percentages.
* Significantly different between the three risk categories.

RESULTS

Sample characteristics

The characteristics of 351 participants are shown in Table 1. The women who did not want to participate in the psychological follow-up study did not differ significantly from the women who did participate, with respect to age and risk status. The three objective risk categories were not equally represented; 11.4% (n=40) of the sample was *BRCA1* or *BRCA2* mutation carrier, 56.7% (n=199) of the women belonged to category 2, and 31.9% (n=112) belonged to risk category 3. The mean age of the total group of women was 40.5 years (range 21-63 years). Age did not significantly differ between the three risk categories. The mean duration of adherence to a surveillance programme was 5.3 years (range 0-30 years). Women in category 1 showed significantly shorter adherence to surveillance than women in the other 2 categories (3 years and around 5.5 years, respectively) ($P < 0.004$). Post-hoc comparisons of the three categories resulted in a statistical significant difference between the following categories: 1 versus 2 and 1 versus 3 (Bonferroni's correction was applied). Most women had a middle level education (54%, n= 188). Most of the women (88%, n= 308) had a relationship and 72% (n=251) had one or more children.

Relationship between risk perception and risk categories

In risk category 1 more than half (60%) accurately estimated their own risk of developing breast cancer (Table 2). Due to the format of the cognitive risk perception question, it was impossible for women in category 1 to overestimate their risk. Underestimation in this category was therefore 40%. In risk category 2, slightly more women underestimated their personal breast cancer risk compared with those accurately estimating it (47.2% and 43.7%, respectively). Overestimation occurred in 9.1% of the women in this category. In risk category 3, 33.3% of the women had an accurate estimation of their own risk, as opposed to 25% underestimating it and 41.7% overestimating it. For the total sample, an accurate risk estimate

Table 2. Accurate risk estimation divided by risk category

Risk category	Underestimation of own risk	Accurate estimate of own risk	Overestimation of own risk
Category 1	40.0%[a]	60.0%	Does not apply
Category 2	47.2%	43.7%	9.1%
Category 3	25.0%	33.3%	41.7%
Total sample	39.4%	42.3%	18.3%

[a] Percentages indicate row percentages, $P < 0.001$ (linear-by-linear association).

was given by 42.3% of the women. The differences between accurate estimation, over- and underestimation in the three risk categories were significant ($P < 0.001$). Additionally, cognitive risk perception distinguished by risk category was related to affective risk perception. The estimated means, adjusted for the co-variables, are shown in Figure 2. Both risk category and cognitive risk perception were significantly related to affective risk perception ($F = 26.8$, $P < 0.001$ and $F = 86.3$, $P < 0.001$, respectively). When testing for a possible interaction between risk category and cognitive risk perception in relation to affective risk perception, we found a non-significant result ($F = 2.5$, $P < 0.07$).

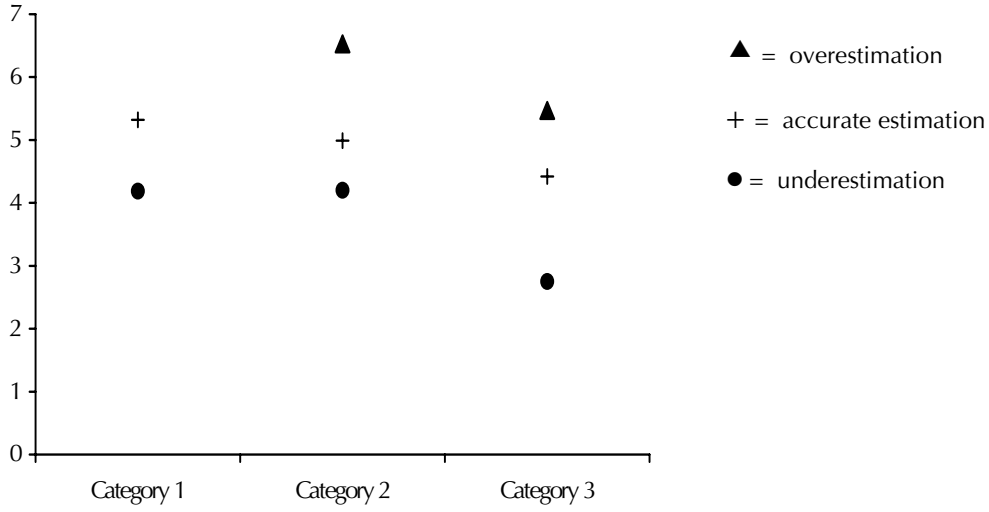

Figure 2. Mean scores (were adjusted for the covariables) on affective risk perception for each risk category distinguished by cognitive risk perception. Mean scores numbers on the Y-axis correspond with the answer categories of the affective risk perception question: 1 = very small, 2 = small, 3 = reasonably small, 4 = not small, not high, 5 = reasonably high, 6 = high, 7 = very high.

Table 3a. Association between cognitive risk perception and general and breast cancer-specific distress (n = 345)

Variable	General distress		Breast cancer-specific distress	
	β[a]	P-value	β[a]	P-value
Underestimation	0.004	0.95	-0.05	0.39
Overestimation	0.09	0.16	0.16	0.02

[a] Standardised regression coefficient as a measure of relative importance.

Table 3b. Association between affective risk perception and general and breast cancer-specific distress (n=344)

Variable	General distress		Breast cancer-specific distress	
	β[a]	P-value	β[a]	P-value
Affective risk perception	0.22	0.002	0.16	0.02
Underestimation	0.09	0.16	0.007	0.92
Overestimation	0.01	0.95	0.10	0.13

[a] Standardised regression coefficient as a measure of relative importance.

Psychological distress in relation to cognitive and affective risk perceptions

The association between cognitive risk perception and general distress was non-significant. However, the association between overestimation and breast cancer-specific distress was significant ($\beta = 0.16$, $P < 0.02$) (Table 3a). Women overestimating their risk reported relatively more breast cancer-specific distress. Furthermore, significant positive associations were found for affective risk perception with both breast cancer-specific distress ($\beta = 0.16$, $P < 0.02$) and general distress ($\beta = 0.22$, $P < 0.002$) (Table 3b). The association between overestimation and breast cancer-specific distress was no longer significant after adding affective risk perception to the regression model ($\beta = 0.10$, $P < 0.13$). This means that, regardless of accurate estimation, overestimation or underestimation, women who had a higher affective risk perception showed higher scores for general distress and breast cancer-specific distress.

DISCUSSION

Our findings underscore Hopwood's notion that the affective risk perception is important (13) and is profoundly associated with psychological distress. Moreover, this association remains irrespective of the accuracy of risk perception.

Less than half of the women in our sample accurately estimated their personal risk of developing breast cancer. Underestimation of risk was most prominent in risk category 2, whereas overestimation was most prominent in risk category 3. Several factors can explain this observation. First, this effect may be a consequence of the genetic counselling. Women in risk category 1 received extensive counselling, with the inclusion of comprehensive information and a written summary of the consultation. The risk figures provided are rather definite and

exact. More than half of this subsample (60%) reported an accurate risk perception, which could reflect a good memory and recall of clear data. Information about an elevated risk of developing breast cancer in the categories 2 and 3 is more complex and less concrete, and may therefore not be discussed as thoroughly, and/or remembered as accurately. Second, women in category 2 who received inconclusive DNA-test results (i.e., a *BRCA1/2* mutation could not be identified) may have previously anticipated a higher risk in accordance with a *BRCA1/2* mutation. Subsequently, the underestimation of the remaining personal risk may reflect their relief at not being identified as a mutation carrier. Moreover, the women who were not identified as a mutation carrier were not offered prophylactic surgery as an option, and this may have prompted additional relief in the patient. The opposite may be true for women in category 3 who may have had no separate genetic counselling and mostly were not given written information. Their knowledge about their elevated risk is not assuaged by a favourable DNA result for *BRCA1/2*. Further, self-selection may play its part in the way that women in category 3 overestimating their risk may be more eager to enrol in a surveillance programme than those who are less worried. Third, the format of the answer categories may have influenced the observed results. Having a relatively higher risk implies that the chance to estimate it lower is higher. When the objective risk is relatively lower, there is a higher chance to overestimate it. Due to the format of the answer categories, it is impossible to become an overestimator in risk category 1, because the greatest chance i.e., *greater than 1 in 2* is the accurate answer for women in this category.

Women who reported breast cancer-specific distress overestimated their objective risk. However, a higher awareness of (affective) risk was associated with both breast cancer-specific and general distress, independent of the adequacy of risk estimation. Women carrying a *BRCA* mutation (risk category 1) who underestimated their risk had a relatively lower affective risk perception which was associated with lower distress scores for both general and breast cancer-specific distress. This observation may reflect denial or minimisation of their elevated risk, in order to protect themselves against (unnecessary) worries. However, these women, in spite of their underestimation and possible denial as a way of self-protection, continue to adhere to the surveillance programme. Indeed, otherwise they would not have been included in this psychological follow-up study. So, in our study sample we did not find indications that the lower distress scores result in a lack of motivation to adhere to recommended guidelines, in contrast to the conclusions of Lerman and colleagues (32).

In a previous study at our institution, we found lower distress scores in mutation carriers opting for surveillance than in mutation carriers opting for bilateral prophylactic mastectomy (33). Mutation carriers with an accurate risk perception showed a mean affective risk perception of 'reasonably high' (Figure 2) indicating a relatively low distress, which is consistent with the lower distress scores of mutation carriers opting for surveillance in the study conducted by Lodder and colleagues. This suggests that women adhering to the surveillance programme feel comfortable and, possibly, are confident that an eventual breast tumour will be detected at an early stage. It is interesting to note that 8 mutation carriers with an accurate cognitive risk perception had an affective risk perception of 'very high', indicating a higher psychological distress. It is possible that these women are in the middle of a decision-making process about an eventual mastectomy. Van Dijk and colleagues recently reported that a higher perceived risk and more breast cancer worry were both significantly associated with the intention to

undergo a prophylactic mastectomy (34).

In all three risk categories, a considerable number of women had inaccurate risk perceptions, either an underestimation or overestimation. How much effort should be made to improve the perception of these women? Despite this level of inaccuracy, all women were adhering to regular surveillance. Inaccurate risk perception therefore did not seem to adversely influence health behaviour. However, from this study, it is not clear how many women do not adhere to screening, or do not even come forward for risk assessment.

Our study showed the importance of affective risk perception and the lesser relevance of adequate risk estimation with regard to distress. Counselling should address the way in which women process information about their given risk estimate (the cognitive dimension). Obviously, more attention is needed to achieve tolerable levels of psychological distress (the affective dimension). The study conducted by Hopwood and colleagues showed no significant reduction in cancer worries after risk counselling, implying that it is not sufficient to provide only numerical information (16). Nevertheless, there are studies demonstrating a decrease in psychological distress after genetic counselling (19, 35). Watson and colleagues found that one year after counselling the level of breast cancer worries remained similar, but this worry was significantly less experienced as a problem by the women (12). The different outcomes of these studies may be partly explained by the different content and quality of the counselling. We speculate that a significant reduction in distress can be achieved if the counsellor or psychosocial worker comprehensively addresses the emotional issues associated with breast cancer. The psychological approach should be tailored to specific women experiencing high distress, and is dependent on intellectual resources and motivation, introspective capacities and the support systems of these women. Specific psychological interventions could include psycho-educational programmes, and interventions from a cognitive-behavioural, psychodynamic, or family-system perspective. In this way, women can be helped to come to terms with any problems and find an adequate and creative adjustment. It is important that future studies address the factors that cause a high affective risk perception, which in turn is significantly associated with higher distress. Moreover, both the quality of counselling and intervention strategies should be further studied.

In conclusion, physicians and researchers need to be aware of the importance of the affective component of risk perception. We recommend that future research focuses on the exact relationship between both cognitive and affective risk perception, and psychological distress. Furthermore, interventions to reduce distress to tolerable levels in women with a high affective risk perception need to be developed and studied.

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Impact of screening for breast cancer in high-risk women on health-related quality of life

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ABSTRACT

Background – The effectiveness of intensive surveillance in women at high risk for breast cancer due to a familial or genetic predisposition is uncertain and is currently being evaluated in a Dutch magnetic resonance imaging (MRI) screening (MRISC) study, in which annual imaging consists of mammography and MRI. Unfavourable side effects on health-related quality of life may arise from this screening process. We examined the short-term effects of screening for breast cancer in high-risk women on generic health-related quality of life and distress.
Methods – A total of 519 participants in the MRISC study were asked to complete generic health-status questionnaires (SF-36, EQ-5D) as well as additional questionnaires for distress and items relating to breast cancer screening, at three different time points around screening.
Results – The study population showed significantly better generic health-related quality of life scores compared to age-/sex-adjusted reference scores from the general population. Neither generic health-related quality of life scores nor distress scores among the study sample (n=334) showed significant changes over time. The impact of the screening process on generic health status did not differ between risk categories. Relatively more women reported mammography as quite to very painful (30.1%) compared to MRI. Anxiety was experienced by 37% of the women undergoing MRI.
Conclusions – We conclude that screening for breast cancer in high-risk women does not have an unfavourable impact on short-term generic health-related quality of life and general distress. In this study, high-risk women who opted for regular breast cancer screening had a better health status than women from the general population.

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INTRODUCTION

Women in Western countries have a 8-10% average lifetime risk of developing breast cancer. One of the risk-increasing factors is a family history of breast cancer (1, 2). About 5-10% of all breast cancer cases occur in women with a strong family history, and in the Netherlands approximately 25% of these cases may be attributed to the *BRCA1* and *BRCA2* breast cancer susceptibility gene mutations (3). Several strategies to reduce the risk of breast cancer or breast cancer death may be discussed with *BRCA1/2* mutation carriers and women with a strong family history, such as intensive surveillance, chemoprevention (4) and prophylactic mastectomy (5). Guidelines for surveillance of these women mostly consist of biannual clinical breast examination (CBE), annual mammography and recommendation for monthly breast self-examination (BSE) (6). Alternative imaging techniques like magnetic resonance imaging (MRI) may be useful because of reported high sensitivity in a diagnostic setting (7, 8).

The effectiveness of intensive surveillance in women at high risk for breast cancer is yet uncertain, although preliminary results have been reported (9-13). It is currently being evaluated as part of a large ongoing prospective national MRI screening (MRISC) study in the Netherlands, in which annual imaging consists of mammography and MRI (14). Unfavourable side effects on health-related quality of life (or health status) may arise from the process of screening itself, like pain, discomfort and feelings of anxiety and distress. Several studies have shown that women with normal results after mammography screening experience no important negative psychological consequences, whereas recall because of a false-positive mammogram causes adverse emotional, physical and social effects (15-18). Only one study reported that screening appeared to be less stressful for women with a family history than for those without (18).

This article describes the short-term effects of screening for breast cancer in high-risk women on health-related quality of life, by empirical assessment at various stages in the screening process. It addresses two specific questions: (1) Does the screening process have any impact, negative or positive, on generic health-related quality of life and distress among high-risk women? (2) Do high-risk women who opt for regular screening differ from the general population with respect to generic health-related quality of life?

MATERIALS AND METHODS

MRISC study

The MRISC study, activated at six family cancer clinics in the Netherlands, is an ongoing prospective observational study for women at increased risk for breast cancer due to a familial or genetic predisposition (14). The study was designed to investigate the effectiveness of intensive surveillance and the value of MRI compared to mammography as a screening tool in high-risk women. Women who were already under intensive surveillance and women who came for the first time to the family cancer clinic were asked to participate in the MRISC study. Women with evident symptoms suspicious for breast cancer or previous breast cancer were excluded. Participants visited the family cancer clinic twice a year for surveillance, consisting of biannual CBE and annual mammography and MRI. All women got instructions for monthly

BSE. Since the start of the study in 1999, 1952 women have been included. The first results were recently presented (9). Approval for the MRISC study was obtained from the Medical Ethical Committees of all six participating family cancer clinics. The health-related quality of life study was approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam.

Design of the study on health-status effects of screening high-risk women

Participants in the MRISC study who were under surveillance at the Family Cancer Clinic of the Erasmus MC, Daniel den Hoed Cancer Center were approached for the empirical health-status study either by mail or by their physician at a scheduled visit at the family cancer clinic. Women received written information about the study, including an informed consent form and a form on which they could indicate that they did not want to participate. Women could send the appropriate form back in a reply paid envelope. A reminder letter was sent to those women who did not return any form within 4 months.

Health-status data were collected at the time points outlined in Figure 1. At 2 months prior to the scheduled screening visit (consisting of either CBE alone or CBE in combination with mammography and MRI) participating women received their first (baseline) questionnaire (time 0 or T0) by mail. They were requested to fill it in and send it back within 2 weeks. The second assessment (time 1 or T1) took place at the day of the scheduled screening visit, preceding the screening. Post-screening measurement (time 2 or T2) was performed 1 week (in case of CBE alone) or 4 weeks (in case of CBE in combination with mammography and MRI) after screening. By that time all women had been informed whether they had breast cancer or not, including those who received additional diagnostic evaluation after scheduled screening. Women with a screen-detected or interval breast cancer did not receive any questionnaire after the diagnosis. Women who did not return their questionnaire within 4 weeks were sent a reminder.

Health-status measures

Health-related quality of life was defined as the woman's functioning in physical, psychological and social domains. The questionnaire contained the Medical Outcomes Study 36-Item Short Form (SF-36) (19-21) as a generic health profile measure and the EQ-5D as a generic preference-based measure of health-related quality of life (22, 23). In addition it contained the somatic subscale (SOM) of the Symptom Checklist-90 (SCL-90) (24), self-developed screen-specific items (25) and other measures (to be reported elsewhere). We used both the SOM scale and the role-emotional and mental health scales of the SF-36 as measures for distress. In the screen-specific items, women were retrospectively (at T2) asked to grade the pain, discomfort and anxiety experienced during CBE, mammography and MRI. For further details on the health-status measures, we refer to Appendix A.

Finally, the questionnaire contained items on sociodemographic characteristics (including age, marital status, living status (single or together), parity, educational level and employment status) and cancer-related characteristics (the number of years adhering to regular surveillance, frequency of BSE, benign breast symptoms in the past, diagnosis of different type(s) of cancer in the past and family history (mother and/or sister(s) affected with breast cancer)).

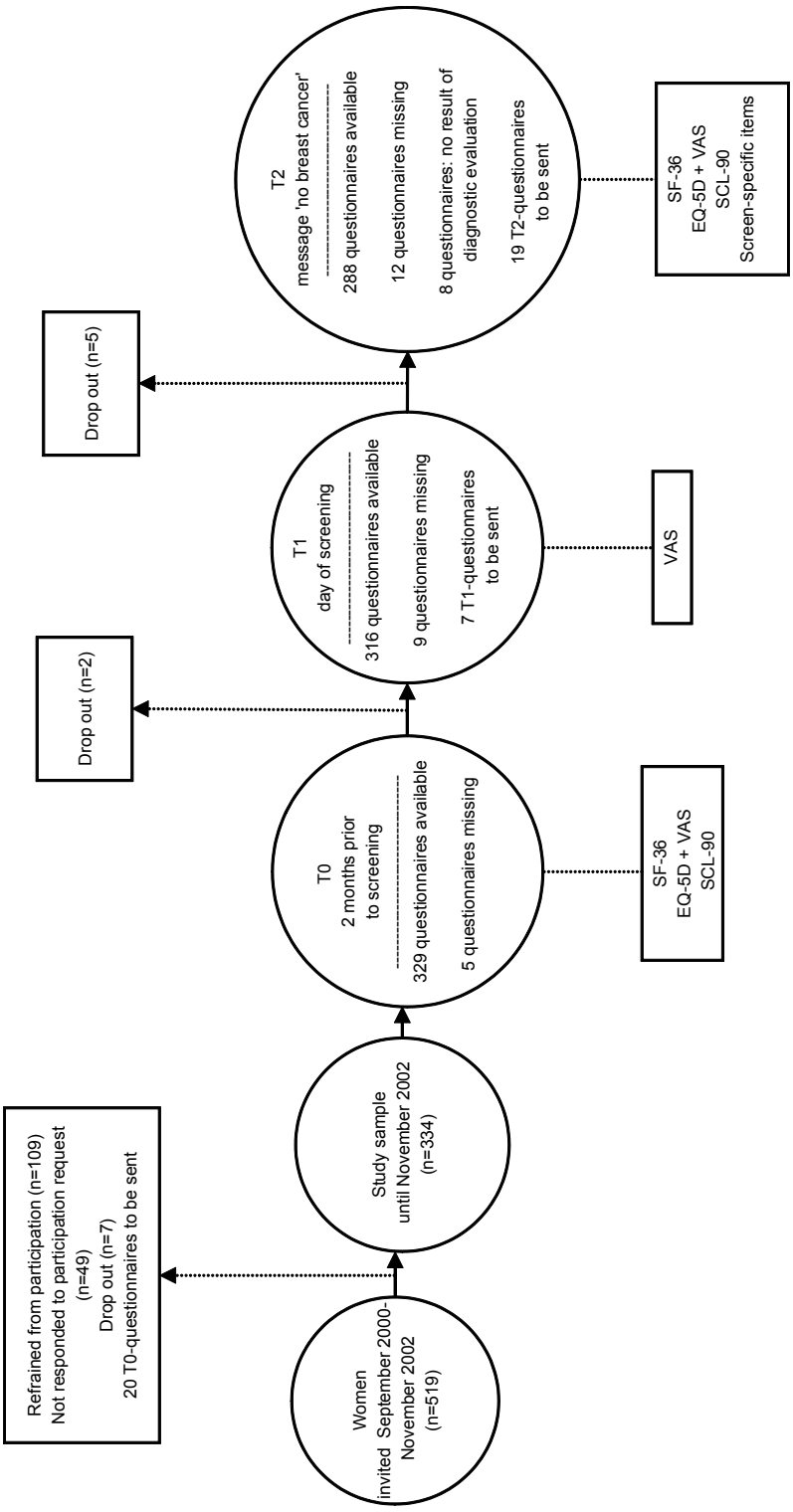

Figure 1. Flow chart describing the number of questionnaires available for statistical analysis (cut-off point November 2002)

Subgroups

Participating women were divided into subgroups according to three criteria. The first was their cumulative lifetime risk (CLTR) for developing breast cancer, based on the tables of Claus (26) and additional information about the family history of ovarian cancer (14). Risk category 1 consisted of *BRCA1/2* mutation carriers (50-85% CLTR), category 2 being women with high risk for breast cancer (30-50% CLTR) and category 3 comprising women with moderate risk for breast cancer (15-30% CLTR). We also distinguished subgroups according to screening modality (two subgroups: CBE alone or CBE in combination with mammography and MRI) and additional diagnostic evaluation after the scheduled screening (two subgroups: yes or no).

Statistical analysis

Missing values for the SF-36 items were imputed according to the standard guidelines (27). No imputation of missing values was applied to the rest of the variables.

Differences in distribution of background variables between the different subgroups were analysed by means of the χ^2 test, Fisher's exact test or linear-by-linear association (nominal and ordinal variables), Student's *t*-test or ANOVA (continuous variables with normal distribution) and by nonparametric procedures (continuous variables without normal distribution: Mann-Whitney or Kruskal-Wallis test). Age- and sex-adjusted reference scores for the SF-36 and EQ-5D were assigned to participating women at T0, based on their age at T0. The one-sample *t*-test was used to test whether the difference between the reference and the observed health-related quality of life scores differed systematically from zero. As only sex- and no age-adjusted reference scores for the SOM scale were available, we analysed the differences between observed SOM scale scores and sex-adjusted reference scores by means of a *t*-test for two independent samples allowing for unequal variances.

To evaluate changes over time in generic health-related quality of life scores (SF-36 and EQ-5D) and in SOM scale scores for the total group of women, we used a repeated measures ANOVA model with time as the only main effect. Differences in health-related quality of life and SOM scale scores between the various subgroups, including differences over time, were also examined with repeated measures ANOVA models. Three models were fitted, each including the main effect for time, and one of the three factors: risk category (model A), screening modality (model B) and additional diagnostic evaluation (model C); all models included the interaction effect for time with one of the three factors. For each model, selection of relevant confounders was done by initially including age and those background variables (Table 1) with a significant ($P \leq 0.10$) difference in distribution between the relevant subgroups as covariates in the model, and then by removing covariates that did not show a significant ($P \leq 0.05$) confounding effect on any of the outcome scores between the subgroups. In all models, we used a compound symmetry covariance structure. The parameters of these covariance matrices were allowed to differ between groups in the models that included one of the three group factors, as this provided for better fitting models.

All P-values resulted from the use of two-sided statistical tests. The data analyses were performed using SPSS (SPSS 10.0.7 for Windows; SPSS Inc., Chicago, IL, USA) or the MIXED procedure of SAS (SAS 8.00 TS Level 00M0 for Windows; SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of the study group

From September 2000 to November 2002, 519 women were approached for the health-status study; 69.6% consented to participate (Figure 1). At November 2002, we had 329 (T0), 316 (T1) and 288 (T2) completed and evaluable questionnaires. Response rates were high among those who received a questionnaire (T0: 98.5%; T1: 96.6%; T2: 94.4%).

Sociodemographic and cancer-related background characteristics of the total study sample and the different subgroups are given in Table 1. The mean age at entry in the study was 40.9 years; 72% of the women had a low to intermediate level of education. The mean number of years already adhering to regular surveillance was 5.4 years, but this differed significantly ($P \leq 0.01$) between the three risk categories. Of the total study sample, 1.6% just started with regular surveillance. Most of the women (88.6%) had (had) a mother and/or sister(s) affected with breast cancer.

No significant differences with regard to age ($P = 0.38$) and CLTR of developing breast cancer ($P = 0.36$) were found between the study sample (n=334) and the women who refrained from participation in the health-status study (n=109). There were also no significant differences with regard to sociodemographic and cancer-related background characteristics and baseline SF-36, EQ-5D and SOM scale scores between the 288 women with a usable T2 questionnaire and the 46 women (334 - 288) without a usable T2 questionnaire, except for the vitality score of the SF-36, which was lower for the women without a usable T2 questionnaire (68.1 vs 60.3, $P \leq 0.05$).

Health-related quality of life over time

The mean score results from the SF-36, EQ-5D and SOM scale at different time points around screening (T0, T1 and T2) are shown in Table 2. For the total group of women, there was a significant ($P \leq 0.01$) but small change in visual analogue scale (VAS) scores over time. A *post hoc* analysis revealed that the mean VAS score at T0 (81.9) differed significantly ($P \leq 0.01$) from the mean T1 score (79.0), which in itself differed significantly ($P \leq 0.05$) from the mean T2 score (80.7). All other generic health-related quality of life scores (SF-36 and EQ-5D utility) and SOM scale scores did not show any significant change over time.

High-risk women showed significantly ($P \leq 0.01$ / $P \leq 0.05$) higher SF-36 scores on most scales as compared to the age- and sex-adjusted SF-36 reference scores from the Dutch (21) and USA (20, 27) general population (Table 2). Also, observed EQ-5D utilities and SOM scale scores among our study sample were significantly ($P \leq 0.01$) more favourable compared to the age- and sex-adjusted EQ-5D utility reference scores from the Swedish general population (28) and sex-adjusted SOM scale reference scores from the Dutch general population (29). Observed VAS scores among our study sample were significantly lower ($P \leq 0.01$) compared to the age- and sex-adjusted reference scores from the Swedish general population (28).

Differences in health-related quality of life between subgroups over time

Covariates included in the final repeated measures ANOVA models were age (models A, B and C), educational level (model B), number of years adhering to regular surveillance (models A and B), frequency of BSE (model A) and mother and/or sister(s) affected with breast cancer (models A and B).

Table 1. Baseline characteristics of participating women at T0 according to risk category, screening modality and additional diagnostic evaluation after screening

		Risk category (n=329)			Screening modality (n=329)		Additional evaluation (n=288)	
	Total (n=329)	50-85% (n=35)	30-50% (n=186)	15-30% (n=108)	CBE (n=163)	CBE +mmg +MRI (n=166)	Yes (n=21)‡	No (n=267)
Age (years)								
Mean (s.d.)	40.9 (8.9)	41.3 (11.0)	41.4 (8.8)	40.0 (8.4)	41.1 (9.3)	40.8 (8.6)	44.5 (8.7)	40.9 (8.9)†
Marital status (%)								
Married / registered partnership	75.5	77.1	77.7	71.3	75.2	75.9	76.2	75.4
Never married	16.8	22.9	13.6	20.4	14.9	18.7	9.5	17.0
Divorced / widowed	7.6	0	8.7	8.3	9.9	5.4	14.3	7.6
Living status (%)								
Living single	10.3	11.8	8.2	13.5	10.6	10.0	14.3	10.9
Living together	89.7	88.2	91.8	86.5	89.4	90.0	85.7	89.1
Parity (%)								
Yes	71.7	60.0	74.7	70.4	70.6	72.9	85.7	70.7
No	28.3	40.0	25.3	29.6	29.4	27.1	14.3	29.3
Educational level (%)								
Low	37.0	45.2	37.6	33.3	45.6	28.7*	31.6	36.6
Intermediate	35.0	25.8	34.1	39.6	31.3	38.7	31.6	36.1
High	27.9	29.0	28.2	27.1	23.1	32.7	36.8	27.3
Employment status: paid job (%)								
Yes	73.7	65.7	74.1	75.7	74.1	73.3	66.7	75.4
No	26.3	34.3	25.9	24.3	25.9	26.7	33.3	24.6
Number of years adhering to regular surveillance								
Mean (s.d.)	5.4 (4.6)	3.0 (1.7)	5.6 (4.6)	5.8 (5.1)*	5.9 (5.1)	4.9 (4.1)†	7.3 (6.0)	5.3 (4.7)
Frequency of breast self examination (%)								
At least once a week	13.5	35.3	10.4	12.0*	12.5	14.5	28.6	11.5
Approximately once a month	57.2	58.8	58.5	54.6	57.5	57.0	52.4	57.6
Approximately once every 3/6/12 months	19.4	5.9	21.9	19.4	18.1	20.6	9.5	21.0
Never	9.8	0	9.3	13.9	11.9	7.9	9.5	9.9
Benign breast diseases in the past (%)								
Yes	38.8	14.3	41.8	41.7*	36.0	41.6	71.4	36.0*
No	61.2	85.7	58.2	58.3	64.0	58.4	28.6	64.0
Diagnosis of different type(s) of cancer in the past (%)								
Yes	4.0	5.7	4.3	2.8	3.7	4.2	4.8	4.2
No	96.0	94.3	95.7	97.2	96.3	95.8	95.2	95.8
Mother and/or sister(s) affected with breast cancer (%)								
Yes	88.6	69.7	93.5	86.0*	93.2	84.1*	95.2	87.8
No	11.4	30.3	6.5	14.0	6.8	15.9	4.8	12.2

CBE = clinical breast examination; mmg = mammography; MRI = magnetic resonance imaging.
* P value ≤ 0.01; † P value ≤ 0.10; ‡ Eight women with additional diagnostic evaluation were excluded from the analyses, because they were still waiting for the results.

Table 2. Observed SF-36, EQ-5D and SOM scale (SCL-90) scores (mean values and 25th-75th percentile score intervals) of participating women at T0, T1 and T2; comparison with (age-/sex-adjusted) reference scores

	T0 (n=329): mean (25th-75th percentile)	T1 (n=316): mean (25th-75th percentile)	T2 (n=288): mean (25th-75th percentile)	Reference scores SF-36: Dutch general population*	Reference scores SF-36: USA general population†	Reference scores EQ-5D‡ and SOM scale§
SF-36 (score 100-0)						
Physical functioning	89.9 (85.0-100.0)	---	89.4 (85.0-100.0)	86.3‖	86.1‖	
Role-physical	85.7 (100.0-100.0)	---	84.1 (100.0-100.0)	77.6‖	82.8	
Bodily pain	82.4 (72.0-100.0)	---	83.0 (72.0-100.0)	72.8‖	75.0‖	
General health perceptions	76.4 (67.0-92.0)	---	77.3 (67.0-92.0)	72.2‖	72.7‖	
Vitality	67.1 (55.0-80.0)	---	68.9 (55.0-80.0)	64.8	59.3‖	
Social functioning	87.7 (75.0-100.0)	---	87.9 (75.0-100.0)	83.5‖	83.0‖	
Role-emotional	85.2 (100.0-100.0)	---	88.1 (100.0-100.0)	80.1¶	81.2¶	
Mental health	76.8 (68.0-88.0)	---	77.7 (68.0-88.0)	74.4¶	73.4‖	
SF-36 summary scores						
Physical component summary	52.5 (49.8-57.7)	---	52.3 (49.2-57.7)	50.0‖	50.7‖	
Mental component summary	51.2 (48.3-57.8)	---	52.2 (48.6-58.0)	50.1	49.1‖	
EQ-5D						
Utility score (score 1-0)	0.88 (0.80-1.00)	---	0.88 (0.80-1.00)			0.85‖
VAS (self-rated health today) (score 100-0)	81.9 (73.0-90.0)	79.0 (70.0-90.0)	80.7 (70.0-90.0)			86.9‖
SOM scale SCL-90 (score 12-60)	17.5 (14.0-19.0)	---	17.1 (13.0-19.0)			18.7**

SOM = somatic subscale; SCL-90 = Symptom Checklist-90; SF-36 = Medical Outcomes Study 36-Item Short Form; VAS = visual analogue scale.
* Age- and sex-adjusted SF-36 reference scores (women of 16-65 years of age) from the Dutch general population (21). Scores were assigned to the sample of participating women at T0, based on their age at T0.
† Age- and sex-adjusted SF-36 reference scores (women of 18-64 years of age) from the USA general population (20, 27). Scores were assigned to the sample of participating women at T0, based on their age at T0.
‡ Age- and sex-adjusted EQ-5D reference scores (women of 20-69 years of age) from the Swedish general population (28). Scores were assigned to the sample of participating women at T0, based on their age at T0.
§ Sex-adjusted SOM scale reference scores (women of 18-83 years of age) from the Dutch general population (29).
‖ Statistically significant (P value ≤ 0.01) difference between observed scores of participating women at T0 and age- and sex-adjusted reference scores (one-sample t-test with test value 0).
¶ Statistically significant (P value ≤ 0.05) difference between observed scores of participating women at T0 and age- and sex-adjusted reference scores (one-sample t-test with test value 0).
** Statistically significant (P value ≤ 0.01) difference between observed scores of participating women at T0 and sex-adjusted reference scores (two independent samples t-test with unequal variances).

The analyses with model A revealed no significant interaction between risk category and time (P-value range 0.16-0.73) for any of the SF-36, EQ-5D and SOM scales. For none of these scales there was a significant main effect of risk category (P-value range 0.12-1.00). The same holds for model B: there were no significant interaction effects between screening modality and time (P-value range 0.15-0.95), and no significant main effect of screening modality (P-value range 0.12-1.00) for any of the outcome scales. Only for the VAS, there was a significant ($P \leq 0.01$) interaction between additional diagnostic evaluation and time (model C). Women without additional diagnostic evaluation after scheduled screening had higher VAS scores at baseline than those undergoing additional diagnostic procedures (83.0 vs 72.4, $P \leq 0.01$), but this difference disappeared at T1 and T2. For the other scales, no significant interaction effects between additional diagnostic evaluation and time (P-value range 0.053-0.87) were seen. There was no significant main effect of additional diagnostic evaluation (P-value range 0.13-0.96) for any of the outcome scales.

Pain, discomfort and anxiety during different screening modalities

Of the women who underwent a screening mammography, 21.1% described pain intensity as 'quite' and 9.0% as 'very' (Table 3). Also 12% of the women reported the MRI to be painful. A large proportion of the women experienced any discomfort during mammography (69.2%) and MRI (45.3%). Anxiety was mainly experienced during MRI, with 10.2% of the total describing anxiety intensity as 'quite' to 'very'.

Table 3. Pain, discomfort and anxiety experienced during relevant screening tests, as reported by participating women in the T2 questionnaire (n=288: 147 women CBE, 141 women CBE+mammography+MRI).

	CBE (n=287)*	Mammography (n=134)*	MRI (n=109)*
Pain (%)			
Not	92.6	14.3	88.0
A little	6.7	55.6	11.1
Quite	0.7	21.1	0.9
Very	0	9.0	0
Discomfort (%)			
Not	91.5	30.8	54.6
A little	7.4	47.4	36.1
Quite	0.7	15.8	4.6
Very	0.4	6.0	4.6
Anxiety (%)			
Not	77.9	72.4	63.0
A little	20.4	22.4	26.9
Quite	1.4	4.5	7.4
Very	0.4	0.7	2.8

CBE = clinical breast examination; MRI = magnetic resonance imaging.
* One of 288 women reported no CBE during last screening; seven of 141 women reported no mammography during last screening; 32 of 141 women reported no MRI during last screening.

DISCUSSION

Intensive surveillance in women at high risk for breast cancer due to a familial or genetic predisposition is increasing. As its effectiveness is yet uncertain, it is important to pay attention to possible unfavourable side effects on health-related quality of life and distress, which may arise from the screening process. As far as we know, no studies had been performed before to investigate the short-term effects of intensive surveillance on health-related quality of life in high-risk women. This study showed that screening women at increased risk for breast cancer, as performed in this study by biannual CBE and annual mammography and MRI, did not have a relevant impact on generic health-related quality of life. Most of the women in our study underwent MRI for the first time.

The results do not provide evidence for a distress-raising effect of screening. The mean SOM scale scores and role-emotional and mental health scores of the SF-36 at 2 months prior and 1-4 weeks after screening did not show any significant difference. There are several possible explanations for this result. First, various coping processes can generate and sustain positive psychological states in the context of highly stressful circumstances, thereby minimizing or avoiding the adverse mental and physical health effects of distress (30). Second, opting for regular screening may give women the feeling that they do everything they can to handle their risk of getting breast cancer, eliminating possible distress-raising effects of screening. Third, the SF-36 was not administered at the day of the screening tests, when distress levels could be elevated. Instead, pre- and post-screening measurement took place 2 months before and 1-4 weeks after screening. Fourth, most of the women adhered to regular surveillance already for a longer time, which may have lowered distress levels. A fifth explanation relates to the method of measuring distress using the SOM scale and the role-emotional and mental health scale of the SF-36, which may be too general. The use of a specific measure of psychological consequences of breast cancer screening could provide additional insight (17, 31).

Interestingly, it appeared that our study population showed significantly better generic health-related quality of life scores (SF-36, EQ-5D utility and SOM scale) as compared to the age-/ sex-adjusted reference scores. It seems that high-risk women who choose for regular screening have a better health status than women from the general population. Most of the women opt for intensive surveillance voluntarily, and this may result in a selection of healthy and well-coping women. This was also seen in the Rotterdam screening trial for prostate cancer, where health status among the voluntary attenders was better than among the general population (25). The difference in health status between our study sample and the general population may partly be due to difference in educational level. Participants in the health-status study appeared to have a significant ($P = 0.03$) higher educational level compared to Dutch women aged 15-64 (32). Individuals with a higher education are more likely to undergo screening (33). Moreover, higher levels of education are also associated with higher levels of quality of life (34).

Women who refrained from participation in the health-status study all opted for intensive surveillance. They did not differ from our study sample with respect to age and risk category. Nevertheless, it is still possible that they differed from our study sample with respect to health-related quality of life, but we had no data available.

Observed VAS scores among our study sample were significantly lower compared to the

age- and sex-adjusted reference scores. This may be caused by the fact that the labelled anchors of the Swedish reference scores were 'dead' and 'full health', instead of 'worst imaginable health state' and 'best imaginable health state' (28).

The VAS score was the only generic health-related quality of life score that showed a significant change over time. However, the absolute differences between the mean VAS scores were small.

Generic health-related quality of life, as well as the impact of the screening process on generic health-related quality of life, did not differ between the three risk categories. These risk categories represent the baseline objective CLTR of developing breast cancer, based on the tables of Claus (26). In these analyses, we did not take into account the women's cognitive or affective perceptions of their risk of developing breast cancer.

Relatively more women reported mammography as quite to very painful (30.1%) compared to CBE or MRI, while a large proportion of the women experienced any discomfort during mammography (69.2%) and MRI (45.3%). The documented incidence of pain associated with screening mammography varies from 1 to 62% (35). Patient education by trained nursing counsellors may reduce mammography-related pain and discomfort (36). Since all mammograms in our study sample were performed at the Erasmus MC, Daniel den Hoed Cancer Center by extremely skilled technicians who inform and support the women, and the majority of the women did not undergo mammography for the first time (contrary to MRI), we think that a lack of information with respect to pain and discomfort experience at mammography is not the issue, rather than the examination itself.

Anxiety was experienced by 37% of the women undergoing MRI. Of the women participating in the MRISC study, 1.8% stopped the study protocol because they refused another MRI or were anxious for the MRI exam (unpublished data).

We did not investigate the impact of additional diagnostic work-up on generic health-related quality of life during recall. There is evidence that recall after a false-positive mammogram causes elevated levels of anxiety and breast cancer worries, even after receiving reassurance that all is well (16, 17). More research on this item is warranted.

Besides intensive surveillance, prophylactic mastectomy is an alternative risk reducing strategy, especially for *BRCA1/2* mutation carriers (5). In the Family Cancer Clinic of the Erasmus MC, approximately half of the unaffected *BRCA1/2* mutation carriers opts for prophylactic mastectomy (37). However, the use and accessibility of prophylactic surgery differs largely between countries (38). Results from studies on the impact of prophylactic mastectomy on generic health-related quality of life are not available in the literature. Utility ratings of prophylactic oophorectomy and mastectomy seem low, although reduction in anxiety was not taken into account (39). Lodder et al. (40) showed that women opting for prophylactic mastectomy had significant higher distress levels than mutation carriers who opted for surveillance, but their distress levels decreased significantly 6 months or longer after surgery, possibly due to the significant risk reduction of developing breast cancer.

We conclude that the screening process does not have an unfavourable impact on short-term generic health-related quality of life and general distress in women at high risk for breast cancer. In this study, high-risk women who opted for regular breast cancer screening had a better health status than women from the general population, which may partly be due to difference in educational level.

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APPENDIX A

Health-status measures

The SF-36 (19) includes eight multi-item scales: physical functioning, role limitations due to physical problems (role-physical), bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems (role-emotional) and mental health. It produces a health profile with scores between 0 and 100 for each dimension, with higher scores indicating a better health status (27). Two summary scale scores can be computed that aggregate the eight scales: the physical component summary and the mental component summary. These summary scores have a mean score of 50 (s.d. = 10) for the general United States population (20). We used a validated Dutch version of the SF-36 (21, 41) with a time frame (reference period) of 1 week.

The EQ-5D (22) is a five-item self-classifier with regard to mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item has three levels: no problems (1), some problems (2) and extreme problems (3). The derived health state descriptions can be linked directly to empirical valuations of health states by the general population, generating utilities that can be used in the calculation of quality adjusted life years (23). The EQ-5D also contains a VAS on which respondents rate their own health between 0 (labelled as 'worst imaginable health state') to 100 (labelled as 'best imaginable health state'). For this study, the standard Dutch EQ-5D was used (42).

The SCL-90 (24, 43) is a self-report symptom inventory for the measurement of psychological distress and psychopathology. The 12-item SOM scale measures complaints about general physical dysfunction as a result of psychogenic or stress-related problems. However, the possibility of actual physical disabilities has to be taken into account. Each item has five levels: not at all (1), a little (2), quite (3), very (4) and extremely (5), providing a total scale score between 12 and 60.

The screen-specific items are self-developed items on experiences during the different

screening tests. They are based on items developed to grade pain and physical discomfort of various prostate cancer screening tests (25). Women were retrospectively (at T2) asked to grade pain, discomfort and anxiety, experienced during CBE, mammography and MRI, respectively. Each item has answer categories on a 4-point Likert scale with labelled end points 'not' and 'very'.

Psychological distress and breast self-examination frequency in women at increased risk for hereditary or familial breast cancer

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ABSTRACT

Background – The Magnetic Resonance Imaging Screening study evaluates the efficacy and psychological impact of a surveillance program for women at increased risk for hereditary or familial breast cancer in the Netherlands. Surveillance consists of biannual physical examination, annual mammography, annual MRI and monthly breast self-examination (BSE). We examined the association between psychological distress and reported BSE frequency.
Methods – Two months prior to surveillance demographics, BSE frequency, general distress (Hospital Anxiety and Depression Scale and the somatic scale of the Symptom Checklist-90) and breast cancer-specific distress (Impact of Event Scale) were assessed in 316 women (mean age 40.5 years, range 21-63 years).
Results – The majority (57%) reported performing monthly BSE. Ten percent reported never performing BSE, 20% less frequently than once a month and 13% at least once a week. Women below the age of 40 who examined their breasts more frequently than recommended (i.e. at least once a week) were shown to be significantly more distressed than the other women in the sample ($P = 0.03$). These women represented 15% of all the women below the age of 40 years in our study sample.
Conclusions – Higher breast cancer-specific distress scores were observed among younger women who examined their breasts at least once a week. It is important for physicians to be aware of this hypervigilant behaviour, especially since it is correlated with breast cancer-specific distress.

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INTRODUCTION

Breast cancer is one of the most common malignancies in women in Western industrialised countries, where 1 in every 10 women will develop breast cancer during the course of her life. In approximately 5-10% of all breast cancer cases, heredity is suspected. In 1994 and 1995, respectively, the *BRCA1* and *BRCA2* genes were identified (1, 2). Mutations in these genes are inherited in an autosomal dominant way, and mutation carriers have a 60-85% lifetime risk of developing breast cancer (3-5). It is thought that other breast cancer susceptibility genes also play a role, such as CHEK2 (6), but either they have not yet been identified or their role is still not clear. High-risk women may opt for intensive surveillance, generally consisting of yearly mammography, 6-monthly clinical breast examination by a physician and monthly breast self-examination (BSE) (7). The efficacy of surveillance in this group of high-risk women is currently unproven (8, 9). Furthermore, the efficacy of BSE as part of the surveillance remains controversial. In a meta-analysis by Hackshaw et al. (10) it is suggested that regular BSE is not an effective method to reduce breast cancer mortality. However, the studies in this meta-analysis focused mainly on the general population, and did not select samples based on family history or genetic predisposition. Therefore, it is not possible to extrapolate these data to a younger population with an increased risk of developing breast cancer due to a proven or possible genetic predisposition. Indeed, this group of women differs significantly from the general population with respect to breast cancer awareness, because of their experiences with breast (and ovarian) cancer in relatives. As there are no data yet on BSE in this specific group, BSE is still advised as part of the surveillance program for high-risk women in the Netherlands (7).

Several studies have shown that monthly BSE is performed by 15-47% of women with a high risk of breast cancer (11-15). Higher levels of breast cancer-specific distress have been found to be associated with higher rates of BSE frequency (13-16), while higher general distress has been found to be related with infrequent BSE performance (11, 16).

We aimed to obtain more insight into the relationship between psychological distress and BSE frequency in Dutch women who are at increased risk of developing breast cancer and who adhere to regular surveillance. In November 1999, the Magnetic Resonance Imaging Screening (MRISC) study was started in six family cancer clinics in the Netherlands. The MRISC is an observational study to evaluate the efficacy of MRI as compared to mammography in a surveillance program for women at increased risk for hereditary or familial breast cancer (MRISC-part A). A longitudinal psychological follow-up study was started in September 2000 in the Daniel den Hoed Cancer Centre in Rotterdam, one of the six clinics (MRISC-part B). The surveillance program consisted of an annual MRI scan in addition to the annual mammography and biannual physical examination (9). Premenopausal women were recommended to perform monthly BSE after menstruation. Postmenopausal women were recommended to pick a fixed day in the month for BSE. In addition to verbal information provided by the physician, women received an information booklet containing written and illustrated BSE instructions. We hypothesised that too frequent BSE might be associated with high breast cancer-specific distress.

SUBJECTS AND METHODS

Participants

At the time of analysis, the study included a total of 316 women, 289 women from MRISC-A and an additional 27 women adhering to regular surveillance who were not included in MRISC-A. One hundred and nine women from MRISC-A refrained from participation in the psychological follow-up study. At entry, the women did not have a history of breast cancer and had a cumulative lifetime risk (CLTR) of developing breast cancer of at least 15% based on the risk tables of Claus et al. (17). Participants had enough understanding of the Dutch language to fill in the questionnaires, and all gave signed informed consent. Ethical approval was obtained from the Medical Ethical Committee of the Erasmus MC in Rotterdam.

Measures

Demographic variables

Age and duration of adherence to regular surveillance were measured in years. Educational level was divided into three categories, i.e. low, medium and high.

Objective risk status of developing breast cancer

Women were categorised into three risk categories according to their lifetime risk of developing breast cancer by means of genetic epidemiological tables (9). Women in risk category 1 were identified *BRCA1* or *BRCA2* mutation carriers, with a CLTR of developing breast cancer of approximately 60-85%. Women in category 2 had a CLTR between 30 and 50%, and were 1st-degree family members of a proven *BRCA1/2* mutation carrier, who did not opt for the test themselves, or 1st-degree relatives of a breast cancer patient from a non-*BRCA1/2* mutation family or a family where genetic testing had not been performed. Women in category 3 had a CLTR between 15 and 30%. These were women from families with an increased frequency of breast cancer occurrence, or 25% risk carriers in a proven *BRCA1/2* family (8, 9, 18).

Intrusion and Avoidance

Intrusion and avoidance was measured using the Impact of Event Scale. This questionnaire developed by Horowitz et al. (19) comprises 15 items and can be tailored to a specific event, which was 'breast cancer' in this study. The Impact of Event Scale measures two common responses to stressful situations, i.e. avoidance and intrusion, and has four answer categories: not at all (0), seldom (1), sometimes (3) and often (5). The intrusion subscale has a score range between 0 and 35, while the avoidance subscale has a score range between 0 and 40. The Dutch version of the Impact of Event Scale has been subjected to reliability analysis (20); the avoidance subscale had an internal consistency of 0.66 and the intrusion subscale of 0.72.

Anxiety and Depression

The Hospital Anxiety and Depression Scale is a 14-item questionnaire; 7 items are designed to measure anxiety and 7 to measure depression (21). Each subscale has a score range between 0 and 21. Scores ranging from 8 to 10 on a subscale identify 'doubtful cases', while scores of 11

and more identify 'definite cases'. A Dutch reliability study revealed an internal consistency of 0.84 for anxiety, 0.86 for depression and 0.90 for the entire scale (22).

Somatic impact

Somatic impact was measured with the somatic subscale derived from the Symptom Checklist-90. This 12-item list consists of physical symptoms often reported when functional problems occur. Each item has 5 possible answers, i.e. not at all (1), a little (2), quite (3), very (4) or extremely (5), providing a score range between 12 and 60 (23). Internal consistency in the normal population of this subscale is 0.83 (24).

Breast self-examination

BSE frequency was measured with one question: Do you perform breast self-examination regularly in order to detect possible anomalies? The question had six possible answers: no, never; yes, approximately once a year; yes, approximately once every 6 months; yes, approximately once every 3 months; yes, approximately once a month, and yes, at least once a week. This variable was recoded into 4 categories: (1) never; (2) once every 3/6/12 months; (3) once a month, and (4) at least once a week.

Design

This study is part of a longitudinal observational study on the psychological impact and quality of life within the MRISC-A study. The analysis in this article was carried out on the first assessment, 2 months prior to the women's appointment in the clinic. The assessments took place between November 2000 and July 2002.

Procedure

Women participating in the MRISC-A study in the Daniel den Hoed Cancer Centre in Rotterdam were sent a letter informing them about the psychological follow-up study along with an information booklet, informed consent form, a refusal form for women who did not want to participate and a prepaid envelope. Additionally, the physicians handed out the information booklets during the women's clinical examination consultation. After returning the informed consent, women were sent their baseline questionnaire to their home (with a prepaid envelope) 2 months prior to their next surveillance appointment at the family cancer clinic.

Statistical analyses

Participants were compared with the 109 non-participants with respect to age with a t-test for independent samples and with respect to risk category by the χ^2 method (linear-by-linear association). The characteristics of the study sample were tested for differences between the three risk categories by one-way analysis of variance for continuous data and by χ^2 test for ordinal data. The empirical structure of the psychological variables was identified by metric principal component analysis. Subsequently, the dimensional structure was established according to the Varimax criterion (25). The fit of the solution was assessed by the sampling adequacy measure (Kaiser-Meyer-Olkin (KMO) measure) (26). Multiple regression analysis was used to determine the relative importance of explanatory variables in estimating psychological distress. The following covariables were entered in the regression analysis: age, number of years

of adherence to a surveillance program, educational level and risk category. The standardised regression coefficient was used as a measure of the relative importance. The level of significance was set at 0.05 (two-sided). Analysis was carried out using the Statistical Package for Social Sciences (SPSS 11).

RESULTS

Sample characteristics

Characteristics of the study sample are shown in Table 1. There was no significant difference in age (P = 0.42) and risk status (P = 0.25) between women who participated in the follow-up study and the women who did not participate. In this study, the three objective risk categories were not equally represented; 10.4% of women were *BRCA1* or *BRCA2* mutation carriers (risk category 1), 56.3% were in risk category 2 and 33.2% were in risk category 3. The mean age was 40.5 years and did not significantly differ between the three risk categories. The mean

Table 1. Characteristics of the study sample

Variable	Risk category 1 (CLTR 60-85%) (n = 33)	Risk category 2 (CLTR 30-50%) (n = 178)	Risk category 3 (CLTR 15-30%) (n = 105)	Total population (n = 316)
Mean age (SD), years	41.5 (10.7)	40.9 (8.7)	39.5 (8.4)	40.5 (8.9)
Mean number of years adhering to surveillance (SD)*	3.1 (1.7)	5.5 (4.6)	5.8 (5.1)	5.4 (4.7)
Educational level				
Lower level	5 (15)	29 (16)	21 (17)	55 (17)
Middle level	18 (55)	98 (55)	55 (52)	171 (54)
Higher level	10 (30)	51 (29)	29 (28)	90 (29)
BSE frequency*				
(1) Never	---	16 (9)	15 (14)	31 (10)
(2) Once every 3/6/12 months	2 (6)	39 (22)	20 (19)	62 (20)
(3) Once a month	20 (63)	102 (58)	57 (54)	179 (57)
(4) More than once a week	10 (31)	18 (10)	13 (12)	41 (13)
BSE frequency by age†				
(1) Never				
< 40 years				14 (5)
≥ 40 years				17 (5)
(2) Once every 3/6/12 months				
< 40 years				34 (11)
≥ 40 years				27 (9)
(3) Once a month				
< 40 years				81 (26)
≥ 40 years				98 (31)
(4) More than once a week				
< 40 years				23 (7)
≥ 40 years				18 (6)

The numbers may vary due to missing values. Figures in parentheses indicate column percentages.
* Significantly different for the three risk categories.
† BSE frequency by age (split at the median of 40 years) for the total group.

number of years of adherence to a surveillance program in the total sample was 5.4. Women in risk category 1 had adhered significantly less long to a surveillance program than women in the other two categories (3 years and approximately 5.5 years, respectively) (P = 0.016). The majority of women had completed a medium-level education (55%). There was no significant difference in level of education between the three risk categories. Although the majority of the study sample (57%) reported following the recommended guideline for BSE, a considerable proportion did not (43%). Thirteen percent were classed as overperformers, whereas 30% were underperformers, with 20% of women reporting examining their breasts less often than recommended and 10% reporting never examining their breasts themselves. Notably, none of the women in category 1 reported never examining their breasts, and only a minority reported examining their breasts less often than recommended (6%). Overperformance, on the other hand, was most striking in category 1 in comparison with the other two risk categories (31 vs. 10 and 12%, respectively). The reported frequencies of BSE were significantly different between the three risk categories (P = 0.005). Frequencies of BSE were compared for women above and below the median age (40 years). There were no significant differences in the frequency of BSE with respect to age.

Structure determination: metric principal component analysis

Correlations between the psychological variables are shown in Table 2. Metric principal component analysis extracted two components, which accounted for 81% of the variance. The solution appeared to be satisfying (KMO = 0.71) (26). Component I comprised intrusion and avoidance and therefore was characterised as breast cancer-specific distress. Component II comprised anxiety, depression and somatic impact and was characterised as general distress. Rotated component scores are shown in Table 3.

Table 2. Correlations between the psychological outcome variables

	Intrusion	Avoidance	Anxiety	Depression	Somatic scale
Intrusion	1.00	0.001	0.001	0.001	0.001
Avoidance	0.77	1.00	0.001	0.001	0.001
Anxiety	0.48	0.45	1.00	0.001	0.001
Depression	0.26	0.30	0.70	1.00	0.001
Somatic scale	0.29	0.29	0.62	0.59	1.00

Left lower triangle: Pearson correlation matrix. Right upper triangle: P-values (two-tailed).

Table 3. Rotated component matrix

	General distress	Breast cancer-specific distress
Intrusion	0.19	0.92
Avoidance	0.18	0.92
Anxiety	0.82	0.36
Depression	0.88	0.10
Somatic scale	0.84	0.14

Table 4. The importance of BSE in estimating general distress and breast cancer-specific distress (n=276)

Variable	General distress		Breast cancer-specific distress	
	β[1]	P-value	β[1]	P-value
Once every 3, 6 or 12 months	0.1	0.31	-0.08	0.43
Once a month	-0.01	0.95	-0.08	0.44
At least once a week	0.07	0.42	0.05	0.6

Values adjusted for age, number of years of adherence, educational level and risk category. The BSE frequency variable was dummy-coded.
[1] Standardized regression coefficient as a measure of relative importance.

Table 5. The importance of BSE in women younger than 40 years in estimating general distress and breast cancer-specific distress (n=276)

Variable	General distress		Breast cancer-specific distress	
	β[1]	P-value	β[1]	P-value
Women younger than 40 years performing BSE at least once a week	0.03	0.64	0.13	0.03

Values adjusted for age, number of years of adherence, educational level and risk category.
[1] Standardized regression coefficient as a measure of relative importance.

Association between psychological distress and BSE frequency

At first no significant associations between general and breast cancer-specific distress and BSE frequency were found (Table 4). Subsequently, we considered possible age-related effects in combination with BSE frequency. Therefore, we dichotomised age at the median (40 years) into younger than 40 and 40 years or older (Table 1). We combined this variable with overperformance of BSE versus the other categories in order to determine whether these women suffered from psychological distress. Again, general distress showed no significant associations (Table 5). However, breast cancer-specific distress showed a significant positive association with overperformance in women below the age of 40 (P = 0.03).

DISCUSSION

The majority of women (i.e. 57%) in this Dutch study reported a BSE frequency of once a month, as recommended, which is more than the 15-47% that has been reported to date (11-15). Thirteen percent in our study reported a BSE performance frequency of at least once a week, which is similar to the findings of Brain et al. (14). Other studies reported rates of overperformance of between 28 and 33%, but these percentages apply to a BSE performance of more often than monthly, and are not further specified (12, 15). Daily BSE performance by 3 and 8% of women, respectively, was reported in the studies by Epstein et al. (13) and Brain et

al. (14). In the study by Epstein et al. (13), however, all the participants had a first-degree relative diagnosed with breast cancer not more than 6 months before inclusion in the study. This short time period after diagnosis of breast cancer in a relative may have influenced women to perform excessive BSE (13).

In our study, a significant association was found between breast cancer-specific distress and BSE overperformance in women below the age of 40. This group of overperformers experiencing breast cancer-specific distress amounts to 15% of the women younger than 40 years. Why did the younger overperformers in particular report relatively higher breast cancer-specific distress scores? It may be that they are more afraid of developing breast cancer and being affected in their femininity by the breast cancer therapy. Indeed, breasts can be considered an important factor in determining feminine identity, and younger women may rely more on their breasts to feel feminine compared to older women. Furthermore, younger women are more likely to be either in the phase of finding a partner or in the process of starting a family and having children. In these processes, breasts are important with respect to femininity, self-esteem and sexuality or when breastfeeding becomes an issue.

The causality between overperformance of BSE in younger women and breast cancer-specific distress is difficult to determine. As Erblich et al. (15) stated, a vicious circle may develop whereby BSE performance causes breast cancer-specific distress, which in turn results in the need to examine the breasts as often as possible to get momentary reassurance. How can this vicious circle be dealt with? Education about frequency, correctly performing BSE and timing (in premenopausal women) may be needed. Indeed, overperformance has been reported to diminish the accuracy of the examination and can induce unnecessary worries when conducted at the wrong time. Before and during the menstrual period, mammary glands can be swollen and some lumps may be mistakenly considered as a tumour, which can (momentarily) result in more distress (13, 27). Moreover, this can lead to unnecessary additional examinations such as ultrasound, puncture and biopsy (28, 29), which in turn induce further distress and overworry. Some physicians at our institution (the Daniel den Hoed Cancer Centre in Rotterdam) encourage the woman's partner to examine her breasts. This may diminish the psychological distress associated with BSE since the partner may be more able to objectively observe any changes that need professional attention.

Since BSE in the general population has no proven effect on breast cancer mortality (29, 30), some groups argue not to teach high-risk women about BSE at all. As a reflection of this controversy, there are differences in recommending monthly BSE in genetically predisposed women between different countries, partly as a result of differences in cultural norms and values (7, 31). For instance, in France, information and training in BSE will be given only on request because of the uncertain effectiveness and the assumption that it may induce anxiety in these women (31). In contrast with this somewhat paternalistic approach, the Dutch as well as the USA policy still recommend BSE as part of the surveillance program, thus putting the emphasis on the patient's autonomy and control in health care. Furthermore, there are also differences in the uptake of prophylactic mastectomy between cultures and countries. At our institution (the Daniel den Hoed Cancer Centre in Rotterdam), 51% of the unaffected mutation carriers chose prophylactic mastectomy (32), whereas this rate is lower in other cultures and countries (33).

In this respect, we think that the performance and outcome of BSE in genetically predis-

posed women may be different from the data obtained in women from the general population, since these women have been confronted with breast cancer and the disease process in family members. This may have an impact on the women's awareness of breast cancer and on the way these women deal with this knowledge.

An important limitation of this study was that the study sample could neither be considered as representative of the population of high-risk women who adhere to a surveillance program nor of high-risk women in general. Although those who did not participate in the psychological follow-up study did not significantly differ from the participants with respect to age and risk status, this does not guarantee an absence of difference on other items such as psychological distress.

In view of the abovementioned considerations, further research with respect to the value of BSE in high-risk women is warranted. As long as the Dutch guidelines still recommend BSE as part of the surveillance program, our findings are of importance for health care workers, since they show that there is a subgroup of younger women who perform BSE too often and who are more likely to experience breast cancer-specific distress. When recognised, additional counselling and care should be offered and may help to improve the quality of life of the concerned women. Further, our data add to the knowledge of the impact of breast cancer surveillance programs in genetically predisposed women, and may be of use for the development and implementation of the guidelines for this group of women in the Netherlands, as well as in other countries.

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Women's acceptance of MRI in breast cancer surveillance because of a familial or genetic predisposition

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Submitted

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ABSTRACT

Background/Methods – Magnetic resonance imaging (MRI) is a promising screening modality for women at increased risk for breast cancer due to a familial or genetic predisposition. We investigated the experience with MRI and preferences for MRI, mammography or clinical breast examination in 178 women adhering to a breast cancer surveillance programme.
Results – MRI was reported to cause limited bother and to provide the most reassurance of breast cancer being absent in case of a favourable test result.
Conclusions –MRI is acceptable as a screening test for women at increased breast cancer risk and is preferred over mammography.

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INTRODUCTION

Magnetic Resonance Imaging (MRI) of the breast appears to be more sensitive than mammography in women with a familial or genetic predisposition for breast cancer, resulting in detection of breast tumours at an earlier stage (1, 2). We investigated the experiences with MRI and the preferences for MRI, mammography or clinical breast examination among women adhering to a breast cancer surveillance programme in a period when the performance of MRI as a screening test was yet unknown.

MATERIAL AND METHODS

The MRI screening study (MRISC study) is a prospective cohort study designed to assess the efficacy of mammographic and MRI screening in women at increased risk for breast cancer due to a familial or genetic predisposition. Women with >15% cumulative lifetime risk (CLTR) for breast cancer were screened twice a year, with biannual clinical breast examination (CBE) and annual mammography and MRI. Women with evident symptoms suspicious for breast cancer or a history of breast cancer were excluded. A detailed description of the study, started in 1999, was reported elsewhere (1). Within the MRISC study, a study on psychological and health-status effects was performed (3-5). The burden of MRI was assessed alongside in women undergoing MRI, who completed two additional questionnaires; the first in the morning preceding the MRI scan (t1), the second one week after the first (t2). At the time of completion of the questionnaires, the women knew the results of neither mammography nor MRI.

Variables in the first questionnaire included baseline characteristics (age; CLTR of developing breast cancer [three categories; details, see (1)]; previous MRI of the breasts), experienced bother with the timing of MRI (between days 5 and 15 of the menstrual cycle; 2 items with 5 response options, ranging from 'no bother at all' to 'extremely bothersome'), fear to undergo MRI (1 item, 3 response options) and fear for the MRI result (1 item, 3 response options).

The second questionnaire included items on the experienced bother of undergoing the MRI scan and of the waiting period for the result (7 items). Finally, women were asked to express their preference for either CBE, mammography or MRI under the assumption that all screening modalities performed equally well; and the level of reassurance they expected to experience from each test, assuming a favourable result (no abnormalities).

RESULTS

Response rate: of the 182 women invited, 178 completed questionnaires at t1, 178 at t2 (176 completed both, 96.7%). Mean age was 42.8 years (standard deviation 8.4 years, range 25-60 years). 15.1% (n=27) had a CLTR of developing breast cancer of > 50% because of a proven *BRCA1/2* mutation, 53.6% (n = 96) had a 30-50% CLTR and 31.3% (n=56) had a CLTR of 15-30%. 83.7% had had previous MRI scan(s) for early detection of breast cancer.

The timing of the MRI scan was reported as 'rather', 'very', or 'extremely' bothersome by 11.7% of those women for whom this was applicable (n=120). Preceding the MRI scan, 11.2%

Table 1. Experienced burden of MRI scan of the breasts (percentages; n=178)

	Insertion of infusion needle	Lying in the tunnel	Lying on one's belly	Not moving	Being alone	Noise of the machine	Duration of time in the tunnel
No bother at all	37.9%	34.8%	50.6%	24.3%	69.5%	40.9%	38.6%
Some bother	52.5%	43.8%	33.1%	58.8%	16.4%	39.8%	45.5%
Rather, very or extremely bothersome	9.6%	21.4%	16.3%	17.0%	14.1%	19.2%	15.9%

expressed serious worries with respect to undergoing the scan; 5.1 % was seriously worried about the scan result; and 29.8% found the waiting period for the test result 'rather', 'very' or 'extremely' bothersome.

The reported experienced bother on seven aspects of undergoing the MRI scan is shown in Table 1. 'Lying in the tunnel' was reported as 'rather' to 'very' bothersome by 21.4%, implying that 78.6% experienced 'some' bother at most. We did not observe significant differences in reported bother between the three risk groups (data not shown).

Under the assumption that MRI, CBE and mammography performed equally well, 44.4% expressed a preference for MRI as a screening test, 41.4% for CBE and 14.2% for mammography. 64.4% reported that they would feel completely reassured by a favourable MRI result, whereas this was 40.1% for mammography and 27.8% for CBE, respectively.

DISCUSSION

Women adhering to breast cancer surveillance because of a familial or genetic predisposition reported limited bother from undergoing an MRI scan as a screening test. We conclude that the direct burden of MRI was acceptable to the large majority of women, although these results may be affected by the fact that most women in the present study had had one or more previous MRI scans. Women who decided not to have further MRI scans after experiencing a first one were thus excluded. In the MRISC study, 4.7% of women under surveillance refused later screening by MRI because of claustrophobia or other reasons (1).

Yet in ignorance of the favourable test characteristics of MRI (1, 2), MRI was preferred as a screening modality over mammography, and MRI was reported to provide the most reassurance of breast cancer being absent in case of a favourable test. We reported in a previous article that women experienced more pain and discomfort during mammography compared to MRI scanning of the breasts, although MRI was associated with more anxiety (in 10.2% [MRI] versus 5.2% [mammography]) (3). These results are in accordance with the scarce data in the literature (6, 7). Though not directly comparable, the study reported by Liang also suggests that MRI is preferred over routine mammography (8).

We conclude that MRI is acceptable as a screening modality for women at increased breast cancer risk, and is preferred by them over mammography.

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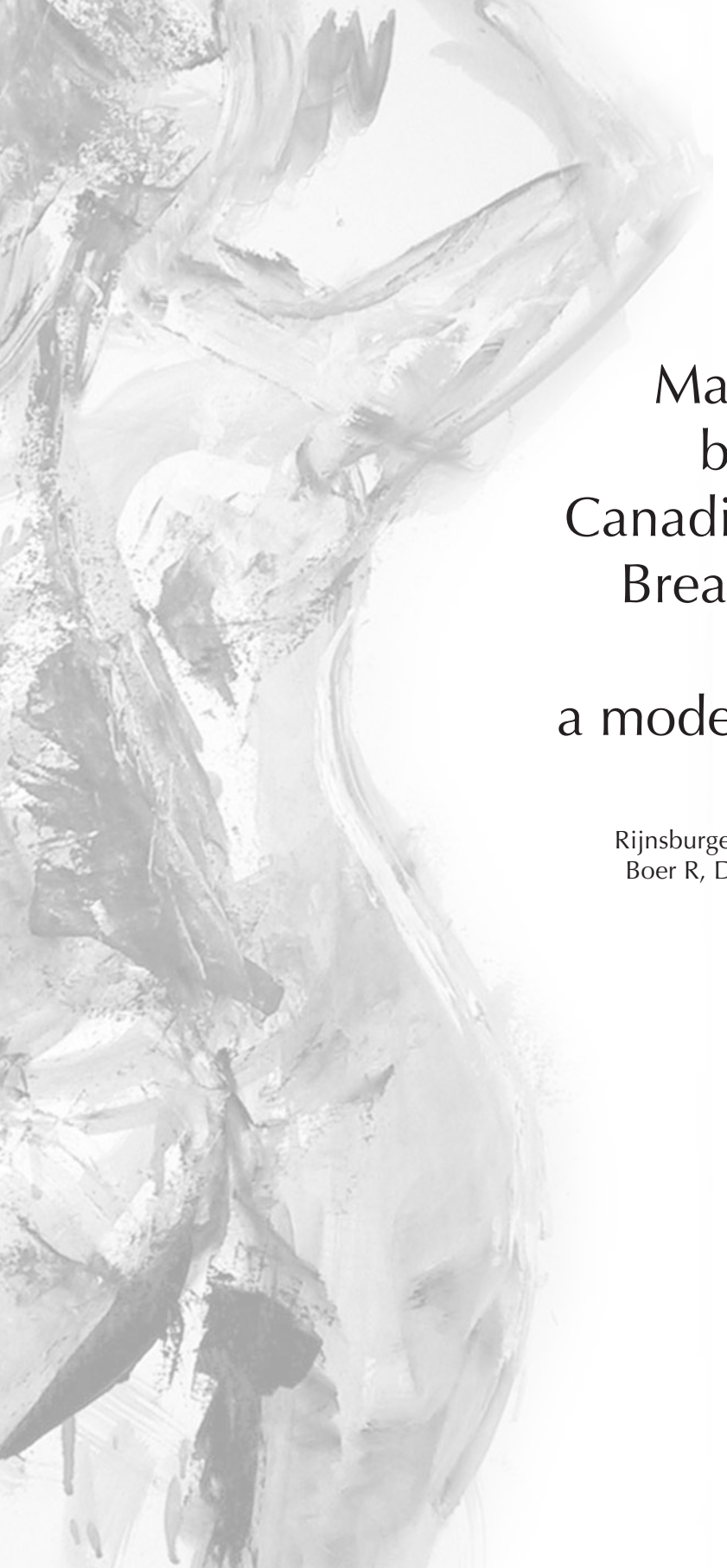
PART II

BREAST CANCER MORTALITY EFFECTS AND COST-EFFECTIVENESS OF SCREENING WOMEN WITH A FAMILIAL OR GENETIC PREDISPOSITION TO BREAST CANCER



Mammography benefit in the Canadian National Breast Screening Study-2: a model evaluation

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ABSTRACT

Background – The Canadian National Breast Screening Study-2 (CNBSS-2) among women aged 50-59 did not show any significant difference in breast cancer mortality between a control arm screened annually by clinical breast examination (CBE) and a study arm screened by CBE and mammography. Because of this design, the benefit of screening compared to no screening could not be evaluated. We therefore conducted a modeling effort to estimate the benefit of mammography or CBE compared to no screening.

Methods – We incorporated demographic, epidemiologic and screening characteristics of the CNBSS-2 in MISCAN. Stage-specific sensitivities of CBE, with and without mammography, and breast cancer incidence rate in the trial were estimated by comparing observed trial data with model predictions. We predicted the number of breast cancer deaths for both study arms of the CNBSS-2 and in the absence of screening, assuming improvement in prognosis by early detection.

Results – We estimated a 24-29% higher breast cancer incidence rate in the CNBSS-2 than the average Canadian rate. Estimated sensitivity of CBE (control arm) varied from 0.29 to 0.48 for stage T1c and from 0.6 to 0.65 for stage T2+. Estimated sensitivity of CBE supplemented with mammography (study arm) varied from 0.5 to 0.79 for stage T1c and was 0.95 for stage T2+. Expected breast cancer mortality reduction by annual CBE screening is 20.5% compared to no screening. Estimated breast cancer mortality reduction by mammography screening compared to no screening for the CNBSS-2 fell within the range 13.6-34.1%.

Conclusions – Enrolled women had above average risk. Screening sensitivity in both arms was high. A benefit of mammography screening is supported by our modeling of the CNBSS-2 results.

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INTRODUCTION

Several randomized controlled trials have assessed the efficacy of mammography screening at reducing breast cancer mortality. An updated overview of 4 Swedish randomized trials showed breast cancer mortality reductions in invited women of 16% (50-59 years) and 33% (60-69 years) (1). However, in a Cochrane review, the authors found smaller breast cancer mortality reductions in 2 so-called medium-quality trials (2). The Malmö trial and the Canadian National Breast Screening Study-2 (CNBSS-2) showed 20% (≥ 55 years) and 3% (50-59 years) breast cancer mortality reductions after 7 years of follow-up.

The CNBSS-2, however, was designed to evaluate the efficacy of annual mammography over and above annual clinical breast examination (CBE). The 7- and 13-year follow-up results of this randomized trial did not show a significant difference in mortality from breast cancer between the 2 groups, even though high detection rates were found (3, 4). Because the control arm was screened, no estimations of mammography benefit compared to no screening could be made, as is available from other mammography trials, nor any estimate of the benefit of CBE screening.

Here, we provide a quantitative interpretation of the CNBSS-2 results, using a MISCAN model evaluation of the trial. MISCAN is a microsimulation program, which has been successfully applied in the evaluation of different cancer-screening programs (5-7). The main purpose of the model evaluation is to show what can be learned about breast cancer screening for women aged 50 and above and about the natural history of the disease from the CNBSS-2 in relation to what we know from other breast cancer-screening trials. The evaluation addresses 2 specific questions: *(i)* Can any explanations, resulting from the model evaluation, be given for the observed equal breast cancer mortality in both study arms of the CNBSS-2? *(ii)* What percentage of breast cancer mortality reduction by mammography screening compared to no screening can we estimate for the CNBSS-2?

MATERIAL AND METHODS

CNBSS-2

The CNBSS-2 is an individually randomized trial in women aged 50-59 years, designed to compare breast cancer mortality following annual screening by both mammography and physical examination of the breasts (MP group) to breast cancer mortality following annual screening by physical examination only (PO group). All participants of both study arms were taught breast self-examination. Women who volunteered for the study with no personal history of breast cancer and no mammograms in the previous 12 months were included. A detailed description of the trial, which started in 1980, and the 7- and 13-year follow-up results have been given elsewhere (3, 4, 8). For the present analysis, we used the CNBSS-2 database, containing records for 39,405 women. We used the number of breast cancers detected at the different screening rounds, number of interval cancers, distribution of tumor characteristics, number of breast cancer deaths (11 years of follow-up), and age distribution and attendance of the trial population. There were small differences in numbers of screen-detected and interval cancers between the CNBSS-2 database and the published CNBSS-2 results (3, 4).

Implementation of demographic, epidemiologic and screening characteristics of the CNBSS-2 in MISCAN

The MISCAN breast cancer-screening model (6, 7) was used to analyze the results of both study arms of the CNBSS-2. A detailed description of the model is given in the Appendix. The PO and MP groups were implemented separately in the model. First, the number of women in each study arm, their age distribution, screening ages, screening interval and attendance rates at successive screening rounds were incorporated. We adjusted the model to the Canadian 1978-1982 clinical age-specific breast cancer incidence data (9) and used the Canadian clinical stage distribution for women aged 50-69 years (10). There was no indication that age- and stage-specific breast cancer survival in Canada differed from that in the Netherlands, so Dutch survival rates were used (see Appendix). The resulting simulated breast cancer mortality rates from MISCAN were comparable to the 1981 Canadian national mortality data (11).

Parameter estimation

In MISCAN, the probability of screen detection is dependent on the sensitivity of the screening test and the age-specific mean durations of the screen-detectable preclinical stages. We started our analysis with a base model in which mean durations are based on analyses of data from the Dutch nationwide screening program (12) (see Appendix).

Stage-specific sensitivities of CBE were derived first (model A) by comparing the observed stage-specific number of screen-detected cancers in round 1, rounds 2-5 and interval cancers in years 1-5 in the PO group with model predictions. Interval cancers are defined as those occurring less than 12 months after a screening examination that did not result in a recommendation for diagnostic evaluation. Numerical optimization with the downhill simplex method (13) was used to find CBE sensitivity estimates that minimize the deviance, calculated by subtracting the log likelihood of the estimated model from the log likelihood of the saturated model and multiplying by 2. A χ^2 test applied to the deviance was used as a test of goodness of fit.

The same procedure was performed for the MP group (model A), resulting in estimated stage-specific sensitivities of CBE supplemented with mammography. We assumed sensitivities of the different invasive stages to be ascending, with a maximum of 0.975 for stage T2+. Invasive cancers without known tumor size were not included in the observed stage-specific numbers, while expected stage-specific numbers were adjusted by the proportion of unknowns. Stage T4 cancers were classified under stage T2+ cancers.

Since women participated voluntarily in the trial, their breast cancer risk might have been different from the average Canadian level. Three alternative model variants were developed: breast cancer incidence rate together with the stage-specific sensitivities of CBE and of CBE supplemented with mammography were estimated in model B, the duration of the screen-detectable preclinical phase T2+ in addition to breast cancer incidence rate and stage-specific sensitivities were estimated in model C, and the total duration of all screen-detectable preclinical invasive stages in addition to breast cancer incidence rate and stage-specific sensitivities were estimated in model D. These parameters were estimated jointly by numerical optimization, minimizing the total deviance statistic for agreement between observed and expected numbers of cancers for the PO and MP groups, calculated as the sum of the individual deviances of both study arms.

Lead time, defined as the time between screen detection and clinical diagnosis in the absence of screening, is generated by MISCAN for every screen-detected case in the model. Mean lead time was estimated for both the PO and MP groups.

Breast cancer mortality

For each of the models (A-D) we predicted breast cancer mortality in the absence of screening, given estimated model parameters (breast cancer incidence rate, durations of screen-detectable preclinical invasive stages) and breast cancer survival. We then predicted the number of breast cancer deaths (1-11 years of follow-up) for both the PO and MP groups of the CNBSS-2, using estimated sensitivities from models A-D. We estimated mammography benefit and CBE benefit, both compared to no screening for the CNBSS-2, and compared predicted breast cancer mortality to observed breast cancer mortality in the CNBSS-2.

Improvement in prognosis after screen detection was defined as 1 minus the ratio of the risk of dying of screen-detected breast cancer divided by the risk if the same cancer had been diagnosed in the absence of screening. We assumed this benefit of early detection to be independent of the screening test used. We first used the improvement in prognosis after screen detection based on the results of analyses of the 5 Swedish mammography screening trials, which was estimated to be 1.000, 0.892, 0.814, 0.567 and 0.395, respectively, for cancers screen-detected in stages DCIS, T1a, T1b, T1c and T2+ (7). The effect of alternative assumptions for the improvement in prognosis after screen detection on expected mortality results (of model C) was also explored. We calculated 95% confidence intervals (CIs) for breast cancer mortality using the Poisson distribution.

RESULTS

Parameter estimates

The upper part of Tables 1 and 2 gives estimated stage-specific sensitivities of CBE supplemented with mammography in the MP group and of CBE alone in the PO group for 4 MISCAN models. The lower part shows the observed number of breast cancers in the CNBSS-2 and the expected number of breast cancers according to the 4 models. In model A, in which breast cancer incidence is assumed to be equal to the average Canadian rate, estimated sensitivities of CBE supplemented with mammography lead to a poor fit of the MP group (Dev = 78.8, 10 df) (Table 1). The same is true for the PO group, where the expected numbers of breast cancers at screen 1 and interval cancers in years 1-5 are much lower than observed (Dev = 28.2, 10 df) (Table 2).

Since the CNBSS is a volunteer trial, breast cancer risk of participants might have differed from the average Canadian level. We estimated breast cancer incidence together with stage-specific sensitivities and found a significantly improved fit [ΔDev (PO + MP) = 49.6, Δdf = 1] for a 40% higher incidence rate (model B). Estimated sensitivities were then, of course, lower compared to model A. However, in model B, there remained a large discrepancy, at both the first and the repeat screenings, between the observed high numbers of screen-detected T2+ cancers in the MP group and the expected numbers, even though the estimated sensitivity of CBE supplemented with mammography is as high as the preset limit (0.975). Furthermore, the

Table 1. Comparison of observed CNBSS-2 results of the MP group with model predictions for different sensitivity estimates of CBE supplemented with mammography, breast cancer incidence rates in the trial, duration of the screen-detectable preclinical phase T2+ and total duration of all screen-detectable preclinical invasive stages.

		Model A *Average Canadian incidence*	Model B *40.0% ↑ incidence*	Model C *29.15% ↑ incidence, 94.82% ↑ duration T2+*	Model D *23.66% ↑ incidence, 115.03% ↑ duration invasive stages*
Sensitivity CBE + mammography					
DCIS		0.771	0.555	0.600	0.635
T1a (≤ 5 mm)		0.600	0.575	0.579	0.322
T1b (6-10 mm)		0.605	0.575	0.586	0.328
T1c (11-20 mm)		0.777	0.720	0.789	0.500
T2+ (> 20 mm)		0.975	0.975	0.953	0.938
	CNBSS-2* observation	Model† expectation	Model† expectation	Model† expectation	Model† expectation
Screen 1, cases of cancer (n)					
DCIS	26	27.7	28.0	27.9	28.2
T1a (≤ 5 mm)	8	2.4	3.2	3.0	3.4
T1b (6-10 mm)	16	10.9	14.7	13.8	14.7
T1c (11-20 mm)	45	24.2	31.7	31.9	35.0
T2+ (> 20 mm)	26	12.9	18.2	30.1	24.8
Total	140	88.1	109.4	122.4	121.7
Screen 2-5, cases of cancer (n)					
DCIS	43	26.5	38.9	35.8	34.1
T1a (≤ 5 mm)	10	9.3	12.9	11.9	13.1
T1b (6-10 mm)	39	34.3	47.4	44.1	42.9
T1c (11-20 mm)	56	36.9	52.3	50.1	60.5
T2+ (> 20 mm)	27	9.3	15.0	17.7	20.4
Total	186	123.8	177.1	169.9	182.5
Interval years 1-5, cases of cancer (n)					
DCIS	2	1.4	3.3	2.8	2.4
T1a (≤ 5 mm)	1	1.8	2.6	2.4	2.3
T1b (6-10 mm)	5	5.8	8.5	7.7	7.4
T1c (11-20 mm)	23	15.9	24.8	20.8	21.4
T2+ (> 20 mm)	15	17.4	26.2	17.4	16.1
Total	54	49.7	76.8	60.0	58.1
Deviance‡		78.8	33.3	21.7	15.3

* Invasive cancers without known tumor size (screen 1: 19; screens 2-5: 11; interval cancers years 1-5: 8) are included in the observed total numbers of cancers but not in the observed stage-specific numbers.
† Expected stage-specific numbers are adjusted by the proportion of invasive cancers without known tumor size, while the expected total numbers are not.
‡ Deviance is calculated as 2 x (log likelihood of the saturated model – log likelihood of the estimated model). The likelihood of the estimated model was calculated assuming the observed number in each stage to be Poisson-distributed, the mean being the number predicted by the model.

Table 2. Comparison of observed CNBSS-2 results of the PO group with model predictions for different sensitivity estimates of CBE, breast cancer incidence rates in the trial, duration of the screen-detectable preclinical phase T2+ and total duration of all screen-detectable preclinical invasive stages

		Model A *Average Canadian incidence*	Model B *40.0% ↑ incidence*	Model C *29.15% ↑ incidence, 94.82% ↑ duration T2+*	Model D *23.66% ↑ incidence, 115.03% ↑ duration invasive stages*
Sensitivity CBE					
DCIS		0.060	0.045	0.053	0.062
T1a (≤ 5 mm)		0.030	0.010	0.008	0.004
T1b (6-10 mm)		0.170	0.145	0.158	0.083
T1c (11-20 mm)		0.550	0.500	0.478	0.287
T2+ (> 20 mm)		0.975	0.970	0.649	0.598
	CNBSS-2* observation	Model† expectation	Model† expectation	Model† expectation	Model† expectation
Screen 1, cases of cancer (n)					
DCIS	4	2.1	2.3	2.4	2.7
T1a (≤ 5 mm)	0	0.13	0.06	0.05	0.05
T1b (6-10 mm)	5	3.5	4.2	4.2	4.2
T1c (11-20 mm)	33	19.6	25.1	22.1	22.8
T2+ (> 20 mm)	20	14.7	20.7	23.4	18.0
Total	65	42.0	54.9	54.7	50.0
Screen 2-5, cases of cancer (n)					
DCIS	3	6.4	6.9	7.5	8.2
T1a (≤ 5 mm)	0	0.49	0.22	0.16	0.18
T1b (6-10 mm)	12	12.1	14.8	14.8	14.3
T1c (11-20 mm)	38	46.1	62.2	54.7	56.4
T2+ (> 20 mm)	27	17.3	26.7	29.9	27.7
Total	86	88.3	119.0	114.9	114.4
Interval years 1-5, cases of cancer (n)					
DCIS	7	6.6	9.5	8.6	8.1
T1a (≤ 5 mm)	2	2.1	3.0	2.8	2.6
T1b (6-10 mm)	15	8.7	12.5	11.4	10.5
T1c (11-20 mm)	27	25.6	38.6	36.2	33.5
T2+ (> 20 mm)	33	23.6	34.9	34.7	32.2
Total	97	76.6	113.6	108.0	100.2
Deviance‡		28.2	24.1	20.9	20.3

* Invasive cancers without known tumor size (screen 1: 3; screens 2-5: 6; interval cancers years 1-5: 13) are included in the observed total numbers of cancers but not in the observed stage-specific numbers.
† Expected stage-specific numbers are adjusted by the proportion of invasive cancers without known tumor size, while the expected total numbers are not.
‡ Deviance is calculated as 2 x (log likelihood of the saturated model – log likelihood of the estimated model). The likelihood of the estimated model was calculated assuming the observed number in each stage to be Poisson-distributed, the mean being the number predicted by the model.

estimated CBE sensitivity of 0.97 for stage T2+ could be considered high.

In model C, we therefore also estimated the duration of the screen-detectable preclinical phase T2+ and found a significantly improved fit [ΔDev (PO + MP) = 14.8, Δdf = 1] for a 29% higher incidence rate and a 95% longer duration of the screen-detectable preclinical phase T2+ (and corresponding estimated T2+ sensitivities of CBE and CBE supplemented with mammography of 0.649 and 0.953, respectively). Instead of estimating the duration of the screen-detectable preclinical phase T2+, we finally estimated the total duration of all screen-detectable preclinical invasive stages (model D). This model also resulted in a significantly improved fit [ΔDev (PO + MP) = 21.8, Δdf = 1] with a 24% higher breast cancer incidence rate, a 115% longer duration of all screen-detectable preclinical invasive stages and estimated sensitivities which were consequently lower.

The average lead time for the MP group was estimated to be 3.6 years (model A), 3.5 years (model B), 4.0 years (model C) and 5.4 years (model D). For the PO group, estimates were 2.3, 2.2, 3.0 and 4.2 years, respectively. According to models C and D, the average additional lead time gained by mammography in the CNBSS-2 was 1.0 and 1.2 years, respectively.

Breast cancer mortality and estimated mortality reduction by screening

In Figure 1*a,b* the observed cumulative numbers of breast cancer deaths in the MP and PO groups are compared to our model predictions, including the estimate for a no-screening policy for the enrolled women, using model C. The expected cumulative numbers of breast cancer deaths in the MP group correspond quite closely to the observed cumulative numbers during the entire follow-up period (Fig. 1*a*), with 91 observed and 87.9 expected (95% CI 69.5-106.3) breast cancer deaths at 11 years (model A 69.8, model B 101.1, model D 76.1). In a situation without screening, we predict 133.4 (95% CI 110.7-156.0) breast cancer deaths after 11 years of follow-up in each arm, using model C (Fig. 1*a,b*). According to this model, the expected breast cancer mortality reduction by annual mammography screening (for 4 or 5 years), supplemented with annual CBE, is 34.1% at 11 years compared to a situation without screening (model A 34.1%, model B 32.6%, model D 32.9%).

Throughout the 11-year follow-up period, the observed cumulative numbers of deaths from breast cancer in the PO group were lower than the cumulative numbers expected by model C (Fig. 1*b*). At 11 years, the total number of observed breast cancer deaths in the PO group was 83 while the model predicted 106.0 (95% CI 85.8-126.1) breast cancer deaths (model A 82.5, model B 118.7, model D 91.0). Using model C, the expected breast cancer mortality reduction by annual CBE screening is 20.5% at 11 years compared to no screening (model A 22.1%, model B 20.9%, model D 19.7%).

The model outcomes for the MP and PO groups lead to an expected relative risk (MP/PO) of dying of breast cancer of 0.829 (95% CI 0.625-1.099) after 11 years of follow-up (model A 0.845, model B 0.851, model D 0.835). The observed relative risk of 1.095 is not significantly different from the model expectation.

Sensitivity analysis

Raising the improvement in prognosis for breast cancers screen-detected at higher stages will probably lower the expected number of breast cancer deaths in the PO group. After changing the improvement in prognosis to 0.575 for all invasive stages, while keeping the total average

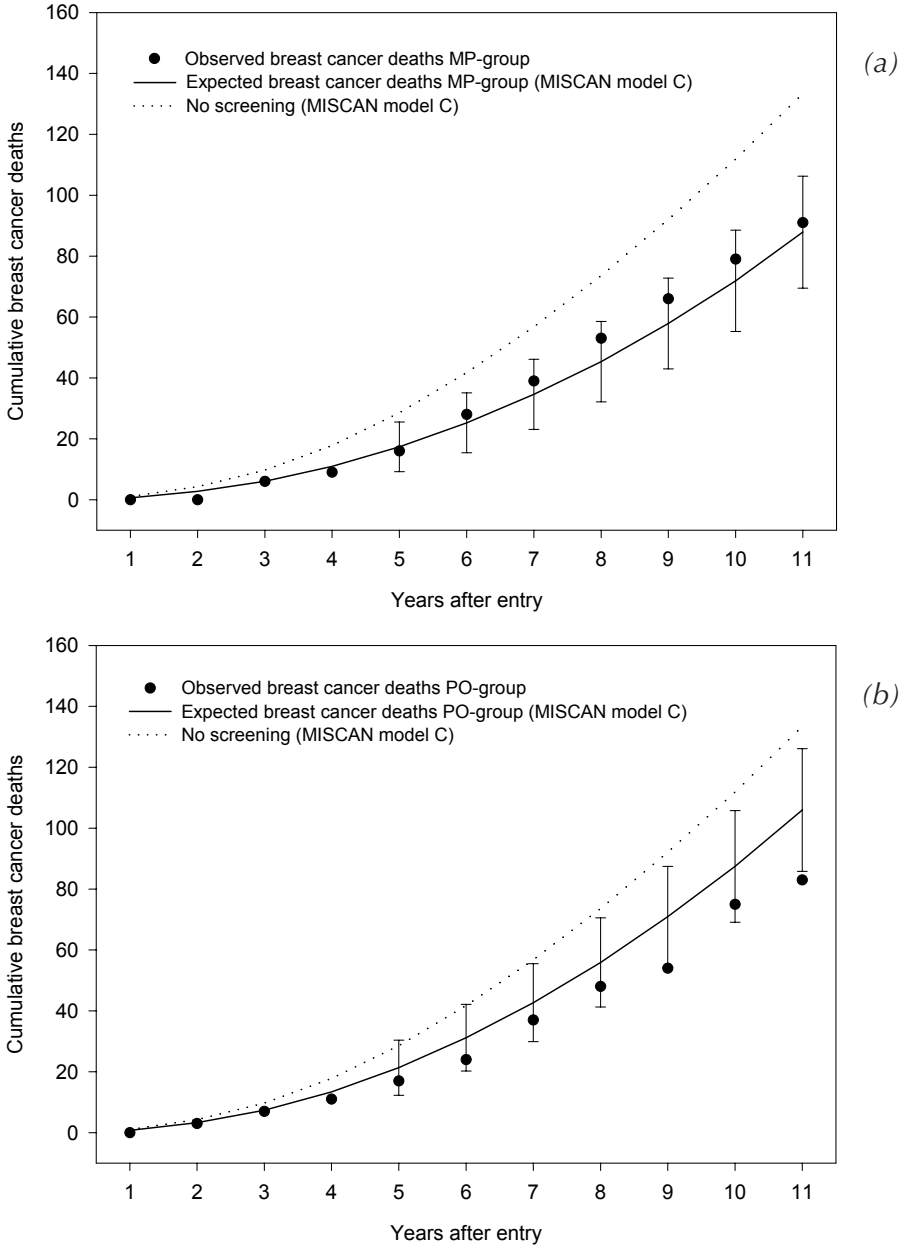

Figure 1 *(a)* Cumulative number of observed (data set*) and expected (model) breast cancer deaths (with vertical bars representing 95% CIs) in the MP group and cumulative number of expected (model) breast cancer deaths in a situation without screening. *(b)* Cumulative number of observed (data set*) and expected (model) breast cancer deaths (with vertical bars representing 95% CIs) in the PO group and cumulative number of expected (model) breast cancer deaths in a situation without screening. (* We used an updated data set with breast cancer deaths known by record linkage with the Canadian National Cancer Registry and National Mortality Database to 31 December 1993 and by active follow-up of breast cancer patients to 30 June 1996.)

improvement in prognosis at the level of the combined Swedish trials (7), the expected (model C) cumulative number of breast cancer deaths in the MP group at 11 years of follow-up stayed consequently at almost the same level (87.3). The model predicted 102.3 breast cancer deaths in the PO group at 11 years of follow-up (95% CI 82.5-122.1). Even with these favorable assumptions for CBE screening, model predictions remain clearly higher than the 83 observed breast cancer deaths in this group.

DISCUSSION

We realize that our model analysis and the CNBSS-2 differ in their approaches. The CNBSS-2 was designed to evaluate the efficacy of annual mammography screening over and above annual CBE, while the primary objective of the model evaluation was to make estimations of mammography benefit and CBE benefit, both compared to no screening, for the CNBSS-2.

Our model analysis shows that the sensitivity of CBE screening in the CNBSS-2 is quite high: 29-48% of T1c and 60-65% of T2+ tumors were detected by CBE. It is known that the CBEs in the CNBSS were performed well. The CBE took 5-10 min and required both visual examination and palpation. It was primarily performed by specially trained nurse-examiners, who were closely monitored during the study (14, 15). High CBE sensitivities for larger tumors are plausible because of this intensive type of screening. However, the quality of CBE in a community setting is likely to be lower (16, 17).

The sensitivity of CBE supplemented with mammography is also high, which contradicts some of the criticisms of mammography quality in the CNBSS (18). However, part of the observed high detection rate at screening is explained by an estimated 24-29% higher breast cancer incidence rate in the trial compared to the average Canadian rate. Because the CNBSS-2 was not population-based, women participated voluntarily. This may have resulted in selection of women with a higher breast cancer risk. Miller et al. (3) identified higher observed breast cancer incidence in the CNBSS-2 than in national data. They calculated the cumulative ratio of observed to expected (based on national data) rates of invasive breast cancer for years 2-5 after entry. In the MP group, this cumulative ratio was 1.28 and in the PO group, 1.18.

The observed breast cancer mortality differential between both study arms (RR = 1.095) is not significantly different from our model expectations (RR = 0.829, 95% CI 0.625-1.099). But our study suggests that annual mammography screening supplemented with annual CBE is expected to reduce breast cancer mortality by 34.1% compared to no screening, while expected breast cancer mortality reduction by annual CBE screening alone is 20.5%. From this we estimate a 13.6% (difference between 34.1% MP group and 20.5% PO group) to 34.1% (difference between MP group and no screening) breast cancer mortality reduction by mammography screening compared to no screening for the CNBSS-2 (50-59 years). While the model predictions of breast cancer mortality correspond quite closely to the observed cumulative numbers of breast cancer deaths in the MP group, the model predicts 28% more breast cancer deaths than observed in the PO group after 11 years of follow-up. Although this difference between observed breast cancer mortality and model predictions for the PO group is unexpected, all observed cumulative numbers of breast cancer deaths in the PO group are within the 95% CI around the model expectation (except for years 9 and 11).

Doubling the duration of the screen-detectable preclinical phase T2+ (model C) or of all screen-detectable preclinical invasive stages (model D) led to a significantly improved model fit. We presented expected breast cancer mortality using model C instead of model D, though the total deviance of model C was higher. However, model D led to mean lead times for the PO and MP groups that were almost 2 years longer compared to our general estimates from other programs (12).

We predicted breast cancer mortality using stage-specific improvement in prognosis after screen detection based on the results of analyses of the 5 Swedish randomized controlled trials (7). Although there has been much discussion about the methodologic quality of several of these trials (2, 19), the general consensus is that their findings are valid (1, 20).

Improvement in prognosis after screen detection was based on breast cancer mortality reductions in women aged 50-69 years (21). However, CNBSS-2 women were 50-59 years old at randomization, and reported effectiveness for this age group is lower (1). On the other hand, CNBSS-2 women were screened annually, while the screening interval in the Swedish trials varied from 18 to 33 months.

The Swedish trials were conducted in an era when adjuvant systemic therapy was not used (22, 23). In contrast, all CNBSS-2 participants had access to such therapy, introduced in Canada in the beginning of the 1980s. This could have influenced survival and improvement in prognosis after screen detection, which we did not take into account.

The duration of the screen-detectable preclinical phase appears to be longer in trial participants than in the general population. One possible explanation for this longer duration is length bias. The trial recruitment procedures discouraged the entry of women with "clinically obvious" breast cancer, who were urged to visit their physician instead. Women enrolled were likely therefore to exclude those with rapidly progressive disease. Also, the volunteer trial may have attracted women who had already had minor breast symptoms for some time but had not yet visited a physician. This could have caused a delay in diagnosis among these women, prolonging the mean duration of the screen-detectable preclinical phase compared to the general population. It seems highly unlikely that the biology of breast cancer in Canadian women, or more specifically in the trial women, is different from our model assumptions, implying another natural history of the disease.

Some uncertainty remains in our model results because of lack of fit of the model. However, in the pooling of data with other mammography screening trials, an estimated breast cancer mortality reduction by mammography screening compared to no screening for women aged 50-59 in the CNBSS-2 of at least 13.6% is plausible. Therefore, the CNBSS-2 can be judged as compatible with the results of other trials of mammography screening.

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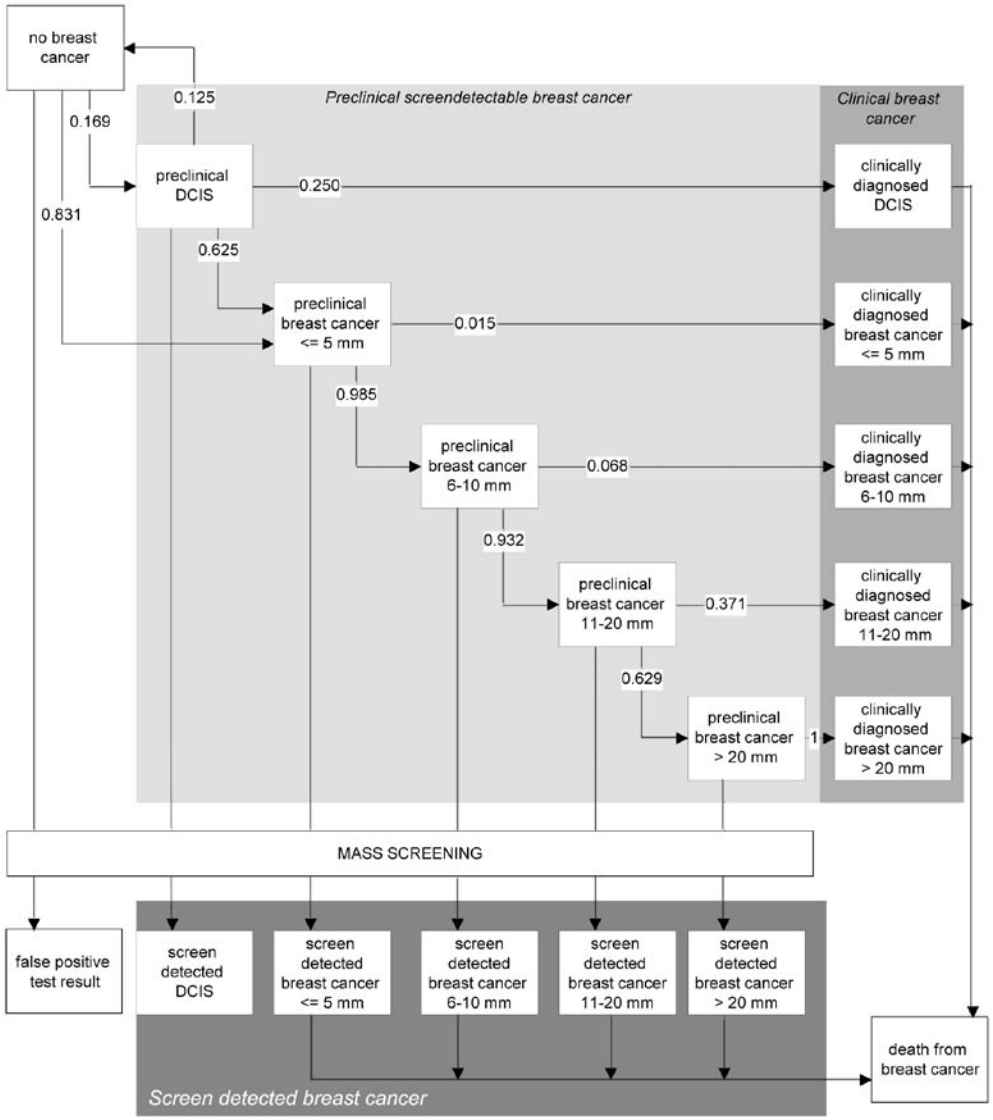
APPENDIX

The MISCAN model

In MISCAN (MIcrosimulation SCreening ANalysis), individual life histories are generated as a Markov process of stages and transitions. The natural history of breast cancer is modeled as a progression through 4 invasive, screen-detectable, preclinical stages according to tumor size: T1a, T1b, T1c and T2+ (≤5, 6-10, 11-20 and >20 mm, respectively). Some of the invasive



Appendix figure. Structure of the MISCAN model for breast cancer, with transition probabilities for age 55 years

cancers are assumed to be preceded by screen-detectable ductal carcinoma in situ (DCIS). Without screening, a preclinical cancer may either be diagnosed clinically or progress to the next preclinical stage. The model generates individual life histories for women, incorporating demographic and epidemiologic characteristics of the (trial) population under study, to calculate the clinical incidence and mortality from breast cancer in a situation without screening. For the situation with screening, screening characteristics (screening ages, interval and attendance rate) and performance of screening are added to the model and screening is applied to the individual life histories of women: preclinical cancers may be detected, depending on the sensitivity of the screening test. In the Appendix figure, the structure of the MISCAN model for breast cancer is presented.

Transitions between stages depend on transition probabilities (Appendix figure, age 55 years) and dwelling time distributions. Durations are generated from exponential distributions with stage- and age-dependent means. The same level of sensitivity is assumed at each screening.

Key parameters in the model of the performance of screening are mean durations of the preclinical screen-detectable stages, sensitivity of the screening test and improvement in prognosis after screen detection. The latter is defined as 1 minus the ratio of the risk of dying of screen-detected breast cancer divided by the risk if the same cancer had been diagnosed in the absence of screening. We assumed this benefit of early detection to be independent of the screening test used. The important base model parameters on natural history and screening, from which we started our analysis, are shown in the Appendix table.

The output of the model contains the number of screen-detected cancers and number of interval cancers (both including stage distribution), clinical age-specific breast cancer incidence by stage and age-specific breast cancer mortality (both with and without screening).

Appendix table. Important base model parameters on natural history and screening in the MISCAN breast cancer model, from which we started our model analysis

Mean duration (years) of screen-detectable preclinical stage by age

	Age (years)			
Stage	*40*	*50*	*60*	*70*
Preclinical DCIS	5.2	5.2	5.2	5.2
Preclinical T1a (tumor ≤ 5 mm)	0.1	0.1	0.1	0.2
Preclinical T1b (tumor 6-10 mm)	0.4	0.5	0.7	0.9
Preclinical T1c (tumor 11-20 mm)	0.8	1.0	1.5	1.8
Preclinical T2+ (tumor > 20 mm)	0.6	0.8	1.1	1.4

Long-term relative survival by clinical stage and age

Age (years)	*DCIS*	*T1a*	*T1b*	*T1c*	*T2+*
40	1.000	0.857	0.787	0.628	0.417
50	1.000	0.855	0.785	0.626	0.412
60	1.000	0.831	0.748	0.562	0.312
70	1.000	0.851	0.777	0.612	0.391

Probability of surviving by time since diagnosis and stage

Time since diagnosis (years)	*Tla*	*Tlb*	*Tlc*	*T2+*
1	0.935	0.951	0.953	0.907
3	0.745	0.854	0.838	0.698
5	0.601	0.627	0.614	0.521
7	0.497	0.481	0.437	0.399
10	0.386	0.295	0.205	0.304
20	0.201	0.182	0.145	0.132
30	0.124	0.108	0.081	0.072
50	0.000	0.000	0.000	0.000

Sensitivity of mammography by stage and age

	Age (years)		
Stage	*40-44*	*45-49*	*≥50*
Preclinical DCIS	24%	32%	40%
Preclinical T1a (tumor ≤ 5 mm)	39%	52%	65%
Preclinical T1b (tumor 6-10 mm)	48%	64%	80%
Preclinical T1c (tumor 11-20 mm)	54%	72%	90%
Preclinical T2+ (tumor > 20 mm)	57%	76%	95%

Reduction in risk of dying of breast cancer by stage in which (pre)cancer is detected

Stage	*Reduction in risk*
Preclinical DCIS	100%
Preclinical T1a (tumor ≤ 5 mm)	89.2%
Preclinical T1b (tumor 6-10 mm)	81.4%
Preclinical T1c (tumor 11-20 mm)	56.7%
Preclinical T2+ (tumor > 20 mm)	39.5%

Clinical breast exams as a screening tool: cost-effectiveness

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Submitted

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ABSTRACT

Background – The usefulness of clinical breast examination (CBE) as a screening modality is uncertain. We explored the cost-effectiveness of CBE when implemented in a nation-wide screening programme, as well as the usefulness of adding CBE to mammography screening.
Methods – The Canadian National Breast Screening Study-2 (CNBSS-2) was simulated with a validated breast cancer-screening model. Stage-specific sensitivities of CBE were estimated by comparing observed trial data and data of a community-based screening programme with various model predictions. We predicted the costs and effects of annual and biennial CBE screening in the Netherlands.
Results – Estimated CBE sensitivity in the CNBSS-2 varied from 0.29 to 0.5 for stage T1c and from 0.6 to 0.97 for stage T2+. Biennial CBE screening in the Netherlands is predicted to prevent 404 to 610 breast cancer deaths per year of screening, compared to 1,155 in the Dutch mammography screening programme. The cost-effectiveness ratio varies from € 1,424 to 2,811 per life year gained, whereas this is € 2,205 in the mammography screening programme. Annual CBE screening is more effective, but less cost-effective than biennial CBE screening. Adding biennial CBE to the Dutch screening programme is estimated to prevent 59 (5.1%) extra breast cancer deaths per year of screening, but the incremental cost per additional life year gained is € 14,015.
Conclusions – We conclude that CBE sensitivity in the CNBSS-2 was high. Biennial CBE screening programmes can be more cost-effective than high-quality biennial mammography screening programmes, but our estimate of reduced effectiveness of CBE advises against its use for screening, either alone or in addition to mammography, in developed countries. For developing countries with relatively low costs for CBE, CBE screening may be an appropriate policy.

Acknowledgements
This study was supported by the Health Care Insurance Board, The Netherlands. We thank Dr. J.K. Bobo for providing information on number of breast cancers detected, with clinical breast examination results and associated mammography findings, among women who reported no breast symptoms at time of screening in the National Breast and Cervical Cancer Early Detection Program.

INTRODUCTION

Randomised controlled trials have shown that breast cancer screening by mammography alone can reduce mortality from the disease. An updated overview of four Swedish randomised trials showed a breast cancer mortality reduction in invited women of 16% (50-59 years) and 33% (60-69 years) respectively (1). Also in service mammography screening programmes a reduction in breast cancer mortality rates is seen (2).

Nowadays mammography screening is almost standard practice, but discussion continues about the effectiveness of clinical breast examination (CBE) in screening programmes. No randomised controlled trial of CBE compared to no screening has been completed (3). Several studies show that CBE has limited additional effectiveness in terms of cancer detection when combined with mammography. The proportion of cancers detected by CBE alone varied from 3.4% in the Edinburgh trial (4), to 3.6% in the DOM-project (5) and 6.7% for women aged 50 to 59 in the Breast Cancer Detection Demonstration Project (BCDDP) (6).

However, other studies suggest a more favourable outcome. CBE as a single screening modality achieved high breast cancer detection rates in the Canadian National Breast Screening Study-2 (CNBSS-2), varying from 3.45 per 1000 at screen 1, to 0.89 – 1.95 per 1000 at subsequent screens (7). When added to mammography, 19% of the breast cancers were detected by CBE alone, averaged over the five screening examinations (7). Further, an evaluation of screening by CBE in the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) suggested that 16% of the breast cancers might not have been detected in the absence of CBE (8, 9).

Recently Bancej et al. showed that the contribution of CBE to the early detection of breast cancer was small, but the question of whether CBE is an effective addition to mammography screening programmes needs further evaluation of the relative costs and benefits as well as the impact on mortality (10).

This article presents model predictions of effectiveness (in terms of breast cancer detection and breast cancer mortality) and cost-effectiveness of CBE screening when implemented in the Dutch nation-wide screening programme. With detailed data from the CNBSS-2 and from a US community-based screening programme (8), we estimated stage-specific sensitivities of CBE, and were able to set these off against sensitivity and cost of mammography screening. The usefulness of adding CBE to mammography screening was also evaluated.

MATERIALS AND METHODS

Canadian National Breast Screening Study-2

The CNBSS-2 is an individually randomised trial in women aged 50-59 years, designed to compare breast cancer mortality following annual screening by both mammography and physical examination of the breasts (MP-group), with breast cancer mortality following annual screening by physical examination only (PO-group). All participants of both study arms were taught breast self-examination. Women who volunteered for the study with no personal history of breast cancer and no mammograms in the previous 12 months were included. A detailed description of the trial and the 7- and 13-year follow-up results have been reported

elsewhere (7, 11, 12). For the present analysis we used the CNBSS-2 database, containing records for 39,405 women. We used the number of breast cancers detected at the different screening rounds, number of interval cancers, distribution of tumour characteristics, and age distribution and attendance of the trial population. There were very small differences in numbers of screen-detected and interval cancers between the CNBSS-2 database and the published CNBSS-2 results (7, 12) (in the order of 1 to 3 breast cancer cases).

Model approach

The MISCAN (MIcrosimulation SCreening ANalysis) breast cancer screening model (13, 14) was used to analyse the results of both study arms of the CNBSS-2, and to predict costs and effects of different population CBE screening strategies. In MISCAN individual life histories are generated as a Markov process of stages and transitions. The natural history of breast cancer is modelled as a progression through four invasive, screen-detectable, preclinical stages, according to tumour size – T1a, T1b, T1c and T2+ (≤ 5, 6-10, 11-20 and > 20 mm respectively). Part of the invasive cancers is assumed to be preceded by a screen-detectable ductal carcinoma in situ (DCIS). Without screening a preclinical cancer may either be diagnosed clinically or progress to the next preclinical stage. The model generates individual life histories for women, incorporating demographic and epidemiological characteristics of the (trial) population under study, to calculate the clinical incidence and mortality from breast cancer in a situation without screening. For the situation with screening, screening characteristics (screening ages, interval and attendance rate) and performance of screening are added to the model, and screening is applied to the individual life histories of women: preclinical cancers may be detected, depending on the sensitivity of the screening test. The same level of sensitivity is assumed at each screening.

Key parameters in the model of the performance of screening are the mean durations of the preclinical screen-detectable stages, the sensitivity of the screening test, and the improvement in prognosis after screen detection. The latter is defined as 1 minus the ratio of the risk of dying of screen-detected breast cancer divided by the risk if the same cancer had been diagnosed in the absence of screening. We assumed this benefit of early detection to be independent of the screening test used.

The output of the model contains the number of screen-detected cancers and number of interval cancers, including their stage distribution, and the clinical age-specific breast cancer incidence by stage and the age-specific breast cancer mortality, for both the situation with and without screening.

Implementation of demographic, epidemiological and screening characteristics of the CNBSS-2 in MISCAN

The PO-group and the MP-group of the CNBSS-2 were implemented separately in the model. First the number of women in each study arm, their age distribution, the screening ages, screening interval and the attendance rates at successive screening rounds were incorporated. We adjusted the model to the Canadian 1978-1982 clinical age-specific breast cancer incidence data (15), and used the Canadian clinical stage distribution for women aged 50-69 years (16). There was no indication that age- and stage-specific breast cancer survival in Canada differed from the Netherlands, so Dutch survival rates were used. The resulting simu-

lated breast cancer mortality rates from MISCAN were comparable with the 1981 Canadian national mortality data (17).

Estimation of stage-specific sensitivities of clinical breast examination

In MISCAN the probability of screen detection is dependent on the sensitivity of the screening test and the age-specific mean durations of the screen-detectable preclinical stages. We started our analysis with a base model in which mean durations are based on analyses of data from the Dutch nation-wide screening programme (18).

Stage-specific sensitivities of CBE were derived first (model A), by comparing the observed stage-specific number of screen-detected cancers in round 1, round 2-5 and interval cancers in year 1-5 in the PO-group with model predictions. Interval cancers are defined as those occurring less than 12 months after a screening examination that did not result in a recommendation for diagnostic evaluation. Numerical optimisation with the downhill simplex method (19) was used to find CBE sensitivity estimates that minimise the deviance, calculated by subtracting the log likelihood of the estimated model from the log likelihood of the saturated model and multiplied by 2. A χ^2 test applied to the deviance was used as a test of goodness of fit.

We assumed sensitivities of the different invasive stages to be ascending, with a maximum of 0.975 for stage T2+. Invasive cancers without known tumour size were not included in the observed stage-specific numbers, while expected stage-specific numbers were adjusted by the proportion of unknowns. Stage T4 cancers were classified under stage T2+ cancers.

Since women participated voluntarily in the trial, their breast cancer risk might have been different from the average Canadian level. To estimate the breast cancer incidence level in the trial, the results of both study arms of the CNBSS-2 were analysed. Three alternative model variants were developed: breast cancer incidence level together with the stage-specific sensitivities of CBE (PO-group) and of CBE supplemented with mammography (MP-group) were estimated in model B, the duration of the screen-detectable preclinical phase T2+ in addition to breast cancer incidence level and stage-specific sensitivities were estimated in model C, and the total duration of all screen-detectable preclinical invasive stages in addition to breast cancer incidence level and stage-specific sensitivities were estimated in model D. These parameters were estimated jointly by numerical optimisation, minimising the total deviance statistic for agreement between observed and expected number of cancers for the PO- and the MP-group, calculated as the sum of the individual deviances of both study arms.

The overall relative sensitivity of CBE compared to CBE supplemented with mammography in the CNBSS-2 was estimated by dividing the expected number of cancers at screen 1 (or screen 1-5) for the PO-group by the expected number of cancers at screen 1 (or screen 1-5) for the MP-group.

As an alternative to parameter estimates based on the CNBSS-2, we also used the study of Bobo et al. (8), which evaluates CBE screening in a community setting (NBCCEDP), to estimate stage-specific CBE sensitivities. Published results report number of screen-detected cancers for both symptomatic and asymptomatic women. We obtained more detailed information for the asymptomatic women by personal communication (J.K. Bobo). Because model C, although with a higher deviance, resulted in more plausible parameter estimates compared to model D, we used the estimated stage-specific CBE sensitivities of model C to derive stage-specific CBE sensitivities among the asymptomatic women in the NBCCEDP.

Estimation of stage-specific sensitivities of mammography supplemented with clinical breast examination

We found that adding CBE to a mammography screening programme led to 4.0% detected breast cancers by CBE alone among asymptomatic women aged 50 years or more in the NBC-CEDP, which was assumed in our further analysis. To estimate the sensitivities of mammography supplemented with CBE, we used the MISCAN breast cancer screening model applied for the evaluation of mass screening for breast cancer in the Netherlands (20, 21). We raised the Dutch mammography sensitivities for the highest breast cancer stages (18) (starting with T2+ and assuming a maximum sensitivity of 0.975 for each stage), until the expected total number of screen-detected cancers contained 4.0% cancers detected by CBE alone.

Costs and effects

The estimated stage-specific CBE sensitivities were used to predict the effectiveness and cost-effectiveness of CBE when implemented in a nation-wide screening programme. We used the MISCAN breast cancer screening model applied for the evaluation of mass screening for breast cancer in the Netherlands (20, 21), and replaced mammography sensitivities by the estimated CBE sensitivities. Improvement in prognosis after screen detection was based on the results of analyses of the five Swedish screening trials, which was estimated to be 1.000, 0.892, 0.814, 0.567 and 0.395 respectively, for cancers screen detected in stages DCIS, T1a, T1b, T1c and T2+ (14). The model output contains the effects of screening in terms of breast cancer mortality reduction and the number of life years gained. Cost-effectiveness (CE) ratios were computed, expressing extra cost per life-year gained by screening. It was assumed that the screening programmes were carried out over a period of 27 years. Costs and effects were computed over 100 years and were adjusted with 3% annual discount rate.

All costs related to screening, assessment and treatment of breast cancer were taken into account (20). The cost of biennial CBE screening was estimated to be 50% of the cost of biennial mammography screening, based on our own exploratory calculations. We used detailed cost analyses for the Dutch nation-wide mammography screening programme (20), and adjusted these for CBE screening. Our cost estimates were higher than those previously published for CBE (22, 23), as they included the full costs of invitations and costs of the nation-wide screening organisation (with tasks like co-ordination, education, quality control and periodic monitoring). We assumed total time required for a CBE to be 20 minutes, including explanation and (un)dressing. In the CNBSS this took 15 to 20 minutes. The cost of annual CBE screening was assumed to be twice as much as the cost of similar biennial screening. Adding CBE to a mammography screening programme was assumed to lead to 25% higher screening cost.

Costs and effects of annual and biennial CBE screening programmes for women aged 50 to 74 years were estimated, including addition to mammography. These results were compared with 2-yearly mammography screening, with mammography sensitivity based on the results of the Dutch nation-wide screening programme (18). All costs and effects are stated as expected differences with a situation where no screening is carried out.

Sensitivity analysis

Eddy assumed the cost of CBE screening to be 33% of the cost of mammography screening (22). Also in the CNBSS the cost of a CBE was estimated to be a third of the cost of mam-

mography (23). Both these estimates included additional costs for organisation of screening, but not as large as those used in our main analysis. The results of this variant (which could apply particularly in countries that cannot afford mammography screening) were shown in a sensitivity analysis.

RESULTS

Sensitivity of clinical breast examination

The upper part of Table 1 gives estimated stage-specific sensitivities of CBE in the PO-group of the CNBSS-2, for four MISCAN models. The lower part shows the observed number of breast cancers in the CNBSS-2, and the expected number of breast cancers for the PO-group according to the four models. In model A, in which breast cancer incidence is assumed to be equal to the average Canadian level, the expected numbers of breast cancers at screen 1 and interval cancers in year 1-5 are much lower than observed, leading to a poor fit of the PO-group (Dev = 28.2; 10 df).

We estimated breast cancer incidence together with stage-specific sensitivities of CBE and of CBE supplemented with mammography, and found a significantly improved fit (Δ Dev (PO + MP) = 49.6; Δ df = 1) for a 40% higher incidence level (model B). Estimated CBE sensitivities were then of course lower compared to model A. However, the estimated CBE sensitivity of 0.97 for stage T2+ could be considered high.

In model C we therefore also estimated the duration of the screen-detectable preclinical phase T2+, and found a significantly improved fit (Δ Dev (PO + MP) = 14.8; Δ df = 1) for a 29% higher incidence level and a 95% longer duration of the screen-detectable preclinical phase T2+ (and corresponding estimated CBE sensitivity of 0.649 for stage T2+). Instead of estimating the duration of the screen-detectable preclinical phase T2+, we finally estimated the total duration of all screen-detectable preclinical invasive stages (model D). This model also resulted in a significantly improved fit (Δ Dev (PO + MP) = 21.8; Δ df = 1) with a 24% higher breast cancer incidence level, a 115% longer duration of all screen-detectable preclinical invasive stages, and estimated CBE sensitivities which were consequently lower.

The estimated (model C) overall relative sensitivity of CBE compared to CBE supplemented with mammography in the CNBSS-2 varied from 45% (screen 1) to 58% (screen 1-5). The overall relative CBE sensitivity among the asymptomatic women aged 50 years or more in the study of Bobo et al. (8) was 34% (J.K. Bobo, personal communication), with most examinations being prevalent screens. The stage-specific CBE sensitivities of model C were lowered by the ratio of these overall relative CBE sensitivities, based on screen 1, to estimate stage-specific CBE sensitivities for asymptomatic women aged 50 years or more in the NBCCEDP (Table 2).

Predicted effectiveness and cost-effectiveness of a CBE screening programme

Table 2 shows the predicted costs and effects of four biennial CBE screening programmes in the Netherlands for women aged 50-74 years, which differ in the estimates for the stage-specific sensitivities of CBE (model B-D and NBCCEDP). Biennial mammography screening is estimated to result in twice to thrice as many breast cancer deaths prevented compared to

Table 1. Comparison of observed CNBSS-2 results of the PO-group with model predictions for different sensitivity estimates of CBE, levels of breast cancer incidence in the trial, duration of the screen-detectable preclinical phase T2+ and total duration of all screen-detectable preclinical invasive stages

		Model A *Average Canadian incidence*	Model B *40.0% ↑ incidence*	Model C *29.15% ↑ incidence, 94.82% ↑ duration T2+*	Model D *23.66% ↑ incidence, 115.03% ↑ duration invasive stages*
Sensitivity CBE					
DCIS		0.060	0.045	0.053	0.062
T1a (≤ 5 mm)		0.030	0.010	0.008	0.004
T1b (6-10 mm)		0.170	0.145	0.158	0.083
T1c (11-20 mm)		0.550	0.500	0.478	0.287
T2+ (> 20 mm)		0.975	0.970	0.649	0.598
	CNBSS-2* observation	Model† expectation	Model† expectation	Model† expectation	Model† expectation
Screen 1, cases of cancer (n)					
DCIS	4	2.1	2.3	2.4	2.7
T1a (≤ 5 mm)	0	0.13	0.06	0.05	0.05
T1b (6-10 mm)	5	3.5	4.2	4.2	4.2
T1c (11-20 mm)	33	19.6	25.1	22.1	22.8
T2+ (> 20 mm)	20	14.7	20.7	23.4	18.0
Total	65	42.0	54.9	54.7	50.0
Screen 2-5, cases of cancer (n)					
DCIS	3	6.4	6.9	7.5	8.2
T1a (≤ 5 mm)	0	0.49	0.22	0.16	0.18
T1b (6-10 mm)	12	12.1	14.8	14.8	14.3
T1c (11-20 mm)	38	46.1	62.2	54.7	56.4
T2+ (> 20 mm)	27	17.3	26.7	29.9	27.7
Total	86	88.3	119.0	114.9	114.4
Interval year 1-5, cases of cancer (n)					
DCIS	7	6.6	9.5	8.6	8.1
T1a (≤ 5 mm)	2	2.1	3.0	2.8	2.6
T1b (6-10 mm)	15	8.7	12.5	11.4	10.5
T1c (11-20 mm)	27	25.6	38.6	36.2	33.5
T2+ (> 20 mm)	33	23.6	34.9	34.7	32.2
Total	97	76.6	113.6	108.0	100.2
Deviance PO-group‡		28.2	24.1	20.9	20.3
Deviance PO- and MP-group‡		107.0	57.4	42.6	35.6

* Invasive cancers without known tumour size (screen 1: 3; screen 2-5: 6; interval cancers year 1-5: 13) are included in the observed total numbers of cancers, but not in the observed stage-specific numbers.

† Expected stage-specific numbers are adjusted by the proportion of invasive cancers without known tumour size, while the expected total numbers are not.

‡ Deviance is calculated as 2 x (log likelihood of the saturated model – log likelihood of the estimated model). The likelihood of the estimated model was calculated assuming the observed number in each stage to be Poisson distributed, with mean the number predicted by the model.

Table 2. Number of screen-detected cancers, mortality effects, costs and cost-effectiveness indices for a) Dutch biennial CBE screening programme with different sensitivity estimates of CBE, and b) Dutch biennial mammography + CBE screening programme. Comparison with the Dutch biennial mammography screening programme and with a situation where no screening is carried out. 3% discount rate and costs in millions € (unless stated otherwise).*

		Sensitivity estimates CBE derived from					
		Model B	Model C	Model D	NBCCEDP		
	No screening	Dutch CBE	Dutch CBE	Dutch CBE	Dutch CBE	Dutch mmg	Dutch mmg + CBE
Sensitivity							
DCIS		0.045	0.053	0.062	0.041	0.400	0.400
T1a (≤ 5 mm)		0.010	0.008	0.004	0.006	0.650	0.650
T1b (6-10 mm)		0.145	0.158	0.083	0.120	0.800	0.890
T1c (11-20 mm)		0.500	0.478	0.287	0.363	0.900	0.975
T2+ (> 20 mm)		0.970	0.649	0.598	0.493	0.950	0.975
Number of screen-detected cancers (x 1,000)†		68.8	61.4	46.7	49.0	116.5	121.3
DCIS		2.6	3.0	3.5	2.3	16.4	16.4
T1a (≤ 5 mm)		0.1	0.1	0	0.1	6.8	6.8
T1b (6-10 mm)		7.2	7.8	4.1	6.0	35.9	39.8
T1c (11-20 mm)		37.0	35.3	22.7	27.9	44.5	46.1
T2+ (> 20 mm)		21.9	15.1	16.4	12.7	12.9	12.3
Detection rate (per 1000 screened)†		2.6	2.3	1.8	1.9	4.4	4.6
		(compared to no screening)					
Deaths from breast cancer†	351,364	-16,476	-14,868	-10,915	-11,842	-31,195	-32,787
Per year of screening†		-610	-551	-404	-439	-1,155	-1,214
Life-years lost from breast cancer (x 1,000)†	6,374	-277	-247	-182	-196	-514	-541
Cost of screening	0	315	315	315	315	629	786
Cost of diagnostics	1,325	-71	-58	-45	-46	-58	-59
Cost of primary treatment	1,887	61	57	38	45	118	125
Cost of follow-up	661	9	7	0	1	43	46
Cost of palliative care	2,487	-155	-139	-102	-111	-286	-301
Total cost	6,360	159	181	205	204	447	598
Deaths from breast cancer	140,520	-8,771	-7,858	-5,781	-6,256	-16,180	-17,022
Life-years lost from breast cancer (x 1,000)	2,395	-111	-99	-73	-79	-203	-213
Cost (€) per life year gained (CE-ratio)		1,424	1,832	2,811	2,596	2,205	2,800

* Screening for women aged 50-74 years and carried out during a period of 27 years. Costs and effects are computed over 100 years.
† Not discounted.

biennial CBE screening. For the less favourable CBE sensitivity estimates of Bobo, only 38% of the breast cancer deaths prevented by biennial mammography screening will be saved.

On average, biennial CBE screening is predicted to prevent 404 to 610 breast cancer deaths per year of screening. The number-needed-to-screen to achieve this result is, on average, 980,000 women per year. Mammography screening is more effective, reducing breast cancer mortality by 1,155 per year of screening. However, in terms of cost-effectiveness, biennial CBE screening can be more cost-effective than biennial mammography screening if the favourable CNBSS-2 sensitivity estimates (model B and C) apply: the CE ratio of CBE ranges

Table 3. Number of screen-detected cancers, mortality effects, costs and cost-effectiveness indices for a Dutch annual CBE screening programme with different sensitivity estimates of CBE. Comparison with the Dutch biennial mammography screening programme. 3% discount rate and costs in millions € (unless stated otherwise).*

	Sensitivity estimates CBE derived from				
	Model B	Model C	Model D	NBCCEDP	
	Dutch CBE	Dutch CBE	Dutch CBE	Dutch CBE	Dutch mmg (biennial)
Number of screen-detected cancers (x 1,000)†	96.8	89.6	71.8	74.8	116.5
DCIS	4.6	5.4	6.1	4.2	16.4
T1a (≤ 5 mm)	0.2	0.1	0.1	0.1	6.8
T1b (6-10 mm)	13.2	14.3	7.6	11.0	35.9
T1c (11-20 mm)	54.6	52.2	36.5	43.3	44.5
T2+ (> 20 mm)	24.3	17.6	21.5	16.2	12.9
Detection rate (per 1000 screened)†	1.9	1.8	1.4	1.5	4.4
	(compared to no screening)				
Deaths from breast cancer†	-23,825	-22,311	-17,154	-18,453	-31,195
Per year of screening‡	-882	-826	-635	-683	-1,155
Life-years lost from breast cancer (x 1,000)†	-403	-374	-287	-308	-514
Cost of screening	629	629	629	629	629
Cost of diagnostics	-94	-80	-67	-67	-58
Cost of primary treatment	87	83	59	69	118
Cost of follow-up	23	21	12	14	43
Cost of palliative care	-225	-209	-161	-173	-286
Total cost	420	444	473	471	447
Deaths from breast cancer	-12,690	-11,812	-9,083	-9,759	-16,180
Life-years lost from breast cancer (x 1,000)	-162	-150	-115	-123	-203
Cost (€) per life year gained (CE-ratio)	2,592	2,962	4,105	3,819	2,205

* Screening for women aged 50-74 years and carried out during a period of 27 years. Costs and effects are computed over 100 years.
† Not discounted.

from € 1,424 to 1,832 per life year gained, compared to € 2,205 in the Dutch mammography screening programme. The lower sensitivity estimates of model D and the NBCCEDP lead to relative high costs per life year gained because fewer breast cancer deaths are prevented and total cost is higher.

The last column of Table 2 contains costs and effects of a biennial mammography screening programme supplemented with biennial CBE. Adding CBE to the Dutch screening programme results in a CE ratio of € 2,800. Per year of screening 59 (5.1%) extra breast cancer deaths will be prevented, at a high incremental cost of € 14,015 per additional life year gained.

Predicted costs and effects of annual CBE screening programmes are presented in Table 3. The number of breast cancer deaths prevented per year of screening ranges from 635 to 882. It is likely that the total cost of annual CBE as a service screening programme in the Netherlands would be approximately as high as the total cost of a mammography screening programme with invitations every two years. This means that annual CBE screening is predicted to be less cost-effective than biennial mammography screening.

Figure 1 summarises the predicted extra costs and life-years gained for the different screening programmes, compared to a situation without screening (3% discounted). The efficient

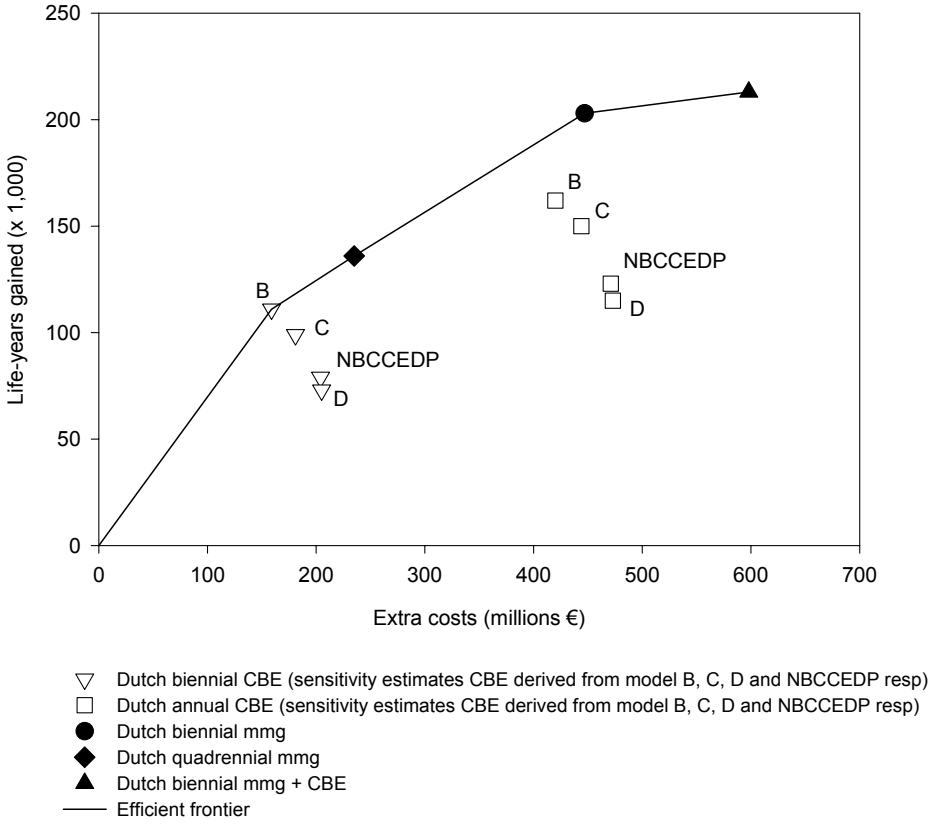

Figure 1. Extra costs and life-years gained for the different screening programmes (3% discounted)

frontier connects Pareto-optimal screening programmes, reached when resources cannot be reallocated to gain more life-years by screening. Annual CBE screening is not a Pareto-optimal screening strategy, because more life-years can be gained by biennial mammography screening without raising costs. Biennial CBE screening programmes can be Pareto-optimal if the CNBSS-2 sensitivity estimates of model B apply (with estimated sensitivity of 0.97 for stage T2+).

Sensitivity analysis

When assuming the cost of biennial CBE screening to be 33% of the cost of biennial mammography screening, the CE ratio of biennial CBE screening ranges from € 482 to 1,375 per life year gained. Assuming the cost of annual CBE screening is twice the cost of similar biennial screening, the CE ratio of annual CBE screening ranges from € 1,298 to 2,283 per life year gained. Using this variant, both biennial and annual CBE screening programmes are more cost-effective than biennial mammography screening programmes, but still of course not more effective.

DISCUSSION

This study shows that biennial CBE screening programmes can be more cost-effective than high-quality biennial mammography screening programmes, but biennial CBE screening is predicted to be 47% to 65% less effective. Annual CBE screening is more effective than biennial CBE screening, but the cost-effectiveness is less favourable because of relative high cost of screening. Adding biennial CBE to the Dutch screening programme is estimated to prevent 59 (5.1%) extra breast cancer deaths per year of screening, but the incremental cost per additional life year gained is € 14,015.

We realise that our model results are based on estimated benefits of early detection derived from the Dutch nation-wide screening programme (18) and from the Swedish trials of mammography screening alone (14). If the apparent breast cancer mortality equivalence of the PO- and MP-group in the CNBSS-2 (12) were to be confirmed by other investigations, then CBE would be even more clearly superior in cost-effective terms.

The model analysis shows that the sensitivity of CBE screening in the CNBSS-2 is quite high: 29% to 50% of the T1c and 60% to 97% of the T2+ tumours were detected by CBE, whereas sensitivity of mammography screening for these stages is 90% and 95%. It is known that the CBEs in the CNBSS were performed well. There CBE included both visual examination and palpation. It was primarily performed by specially trained nurse-examiners who were monitored during the study (24, 25). High CBE sensitivities for larger tumours might be plausible because of this intensive type of screening.

Estimated stage-specific CBE sensitivities among asymptomatic women aged 50 years or more in the community-based screening programme NBCCEDP were lower than estimated CNBSS-2 sensitivities. However, in the NBCCEDP CBE screening was performed under less controlled conditions compared to the trial setting (9). The possibility of high quality CBE screening in a community setting depends on factors such as financial budget, use and availability of professional examiners, use of detailed guidelines, periodic monitoring and quality

control procedures (24, 25). Specific training programmes can improve the CBE accuracy and skills of health professionals (26).

We used the CNBSS among women aged 50-59 to derive stage-specific CBE sensitivities. Because our aim was to predict the effectiveness and cost-effectiveness of CBE when implemented in a nation-wide screening programme for women aged 50-74 years, we did not use the CNBSS-1 results with women aged 40-49 years at randomisation (27).

No randomised controlled trial estimating the benefit of CBE alone compared to no screening has been completed. A case-control study (28) and an ecological study (29) provided weak evidence for a reduction in breast cancer mortality in women screened by CBE as compared to no screening.

We predicted breast cancer mortality by using stage-specific improvement in prognosis after screen detection based on the results of analyses of the five Swedish randomised controlled trials in women aged 50-69 years (14). Although there has been discussion about the methodological quality of several of these trials (30, 31), the consensus is that their findings are valid (1, 3). However, the CNBSS-2 was conducted in an era when adjuvant systemic therapy was routinely applied in Canada for women with stage 2 disease, whereas this did not occur in the Swedish trials (32, 33). Further, CNBSS-2 women were 50-59 years at randomisation, and the recent Swedish overview analysis suggests a lesser effectiveness of mammography alone screening for this age group (1).

In practice, costs may vary for screening programmes using similar screening schedules, depending on several factors. For example, the cost of CBE screening will be lower in developing countries, mainly due to lower salaries and overhead costs. Therefore realistic cost estimates are essential to make accurate predictions of the cost-effectiveness of a CBE screening programme in a specific country. These considerations are important for countries where it is likely that CBE will be far less costly to implement than mammography.

CE ratios for annual CBE have been calculated previously, with the effectiveness of CBE screening based on the results of the Health Insurance Plan (HIP) study and the BCDDP (22). The marginal cost per year of life expectancy for CBE alone ranged from $ 10,000 to 15,000 for women over age 50 and from $ 15,000 to 30,000 for women under age 50 (5% discount rate). As these outcomes are based on screening an individual woman, and not a population of women, the reported results are difficult to compare with our estimated CE ratios.

Mammographic visibility of breast tumours is lower in women under 50 years, because these women have denser breasts (34, 35). As well as lower sensitivity, the false positive rate for mammography is higher compared to women over 50 years (36, 37). CBE could be of potential benefit for younger women, although the false positive rate for CBE increases with declining age (36). However, recent findings suggest that sensitivity of CBE is lower in younger women (38). The effectiveness of CBE screening in high risk women is currently under investigation as part of a large ongoing prospective national MRI screening study in the Netherlands (39).

Our estimate of reduced effectiveness of CBE advises against its use for screening, either alone or in addition to mammography, in developed countries. For developing countries with relative low costs for CBE, CBE screening may be an appropriate policy.

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Screening women with a familial or genetic predisposition to breast cancer: costs and effects of alternative screening policies

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ABSTRACT

Background – A substantial proportion of women has a more than average risk for breast cancer due to a familial or genetic predisposition, for which magnetic resonance imaging (MRI) is a promising screening modality. Estimates on breast cancer mortality reduction of screening these women are lacking, and randomized controlled trials are practically impossible.
Methods – In a prospective cohort study in 1952 women with increased breast cancer risk we estimated stage-specific sensitivity of different screening tests and resulting stage-shift by screen detection. Benefit of early detection was based on modeling estimates and pooled analyses of randomized mammography screening trials. We explored the effectiveness and cost-effectiveness of alternative screening policies for three risk categories: *BRCA1/2* mutation carriers (50-85% cumulative lifetime risk (CLTR)), a high-risk (30-50% CLTR) and a moderate-risk group (15-30% CLTR).
Results – Intensive surveillance including MRI in *BRCA1/2* mutation carriers is estimated to reduce breast cancer mortality by 50.1%, compared to 40.7% by mammography and clinical breast examination (CBE) only. Its effectiveness is almost twice as high compared to mammography screening in women with average risk. Screening *BRCA1/2* mutation carriers with biannual CBE and annual mammography and MRI from age 30 to 60 is at a cost of € 4,314 per life-year gained (3% discounting). Offering MRI and mammography alternately at a 6 months interval is even more cost-effective. For the moderate-risk group, screening regimes with only mammography, alternatively in combination with CBE, from age 40 to 50 years are most favorable in terms of cost-effectiveness (range € 3,080 - € 4,764), and may lead to 24.5-30.7% breast cancer mortality reduction. Observed breast cancer incidence in the high-risk group did not differ substantially from the moderate-risk group.
Conclusions –Including MRI in *BRCA1/2* mutation carriers surveillance is a very cost-effective screening policy, and should therefore be offered. For the moderate-risk category, intensive surveillance without MRI is defendable. Longer study follow-up is needed to advise a screening regime for the high-risk category.

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INTRODUCTION

In most Western countries the average lifetime risk for women of developing breast cancer is 8-10%. Risk-increasing factors are a family history of breast cancer and a germline mutation of the *BRCA1* or *BRCA2* gene (1, 2). Randomized controlled trials have shown that breast cancer screening by mammography can reduce mortality from the disease by about 25% in women aged 50-69 years (3). Although there has been discussion about these trials (4), the general consensus is that their findings are valid (5). Women with increased risk are often diagnosed before the age of 50 years, and effectiveness of mammography screening in this age group is uncertain (6) or limited (7). Moreover, mammographic visibility of breast tumors is lower in women under 50 years (8).

Prospective studies now have shown that intensive surveillance including magnetic resonance imaging (MRI) can detect breast cancer at an earlier stage in women with an inherited susceptibility to breast cancer (9-11). MRI appears to be more sensitive than mammography. However, long-term effectiveness in terms of breast cancer mortality reduction of screening these women is unknown, as well as the cost-effectiveness. MRI is costly and leads to more short-term follow-up imaging and benign biopsies due to lower specificity compared to mammography (9-12).

With screening data from a prospective cohort of 1952 women with increased breast cancer risk (9) we were able to estimate sensitivity and specificity of different screening tests. Screening results in a shift from diagnosing relatively large clinical cancers towards earlier (screen-detected) stages of cancer. We used a well-validated breast cancer-screening model (6, 13, 14) to predict effectiveness (in terms of breast cancer mortality reduction) and cost-effectiveness of alternative screening policies for different risk categories, varying in cumulative lifetime risk (CLTR) for developing breast cancer. Benefit of screening was based on results of randomized mammography screening trials. We investigated which screening regime (in terms of screening age, screening interval and screening tests) is advisable.

MATERIAL AND METHODS

MRI screening study (MRISC study)

The MRISC study is a prospective cohort study designed to assess the efficacy of mammographic and MRI screening in women at increased risk for breast cancer due to a familial or genetic predisposition. Women with >15% CLTR for breast cancer were screened twice a year, with biannual clinical breast examination (CBE) and annual mammography and MRI. The 1952 participants were divided into three subgroups according to their estimated CLTR for developing breast cancer: *BRCA1/2* mutation carriers (50-85% CLTR), a high-risk group (30-50% CLTR) and a moderate-risk group (15-30% CLTR). These CLTR categories for breast cancer were based on modified tables of Claus (15, 16), with risk of developing breast cancer dependent on the number of family members with breast cancer (1, 2 or ≥ 3), their age at diagnosis, whether they were first- or second-degree relatives, and family history of ovarian cancer. Women with evident symptoms suspicious for breast cancer or previous breast cancer were excluded. A detailed description of the study, which started in 1999, has been reported elsewhere (9).

For the present analysis we used the number of screen-detected breast cancers, number of interval cancers, distribution of tumor characteristics, age distribution of the study population and attendance rates at successive screening rounds of the MRISC study, with a median follow-up of 2.9 years.

MISCAN breast cancer-screening model

The MISCAN breast cancer-screening model (6, 14) was used to simulate the MRISC study, and to predict costs and effects of different screening strategies for women with increased breast cancer risk. MISCAN is a well-validated microsimulation model, which has been successfully applied in the evaluation of different cancer-screening programs (13, 17, 18). In MISCAN, the natural history of breast cancer is modeled as a progression through successive screen-detectable, preclinical stages according to tumor size, to clinical disease states. A detailed description of the MISCAN breast cancer model, including principal model parameters used up to now, is given elsewhere (14, 17). On the basis of data from the Dutch nation-wide screening program in women aged 50-74 (19) and regional breast cancer screening projects in women under age 50 (20), natural history is simulated. With screening, diagnosis will shift from clinical cancer towards preclinical stages of cancer, resulting, if earlier treatment is more effective, in a possible decrease in breast cancer mortality. The benefit of this stage-shift, i.e. improvement in prognosis after screen detection, is validated on results of randomized mammography screening trials. Updated breast cancer survival rates according to age, tumor stage and nodal status are incorporated in the model.

We constructed three risk-specific models corresponding to the three risk categories used in the MRISC study (15, 16). These models predicted a lifetime background risk of developing breast cancer of 72.5% for *BRCA1/2* mutation carriers, 40% for the high-risk group and 22.5% for the moderate-risk group (compared to 10% for the general population) and correctly predicted the observed penetrance function i.e. clinical age-specific breast cancer incidence (21). We determined values for the sensitivity of the different screening tests and the mean duration of the preclinical screen-detectable stages.

For assessing the validity of the three risk-specific models, we compared the number of diagnosed breast cancer cases, overall cumulative incidence rate and tumor characteristics as observed in the MRISC study with model predictions. Therefore the number of women in each risk category, their age distribution, screening ages, type of screening tests and screening interval (biannual CBE, annual mammography and MRI), and attendance rates at successive screening rounds in the study were incorporated into each risk-specific model. Likelihood ratio tests were used to compute P-values for goodness of fit.

Sensitivity

The sensitivity of the different screening tests was age- and stage-dependent. For pre-menopausal women (<50 years) we used the relative sensitivities of mammography and MRI derived from the MRISC study results. Mammography sensitivities in women aged 55 and above were based on the results of the Dutch nation-wide breast cancer-screening program (19, 22), with more than 1 million women (50-74 years) invited for screening per year, and 1.08 interval cancers per 1000 woman-years in 1999 (23). Stage-specific sensitivities of MRI in women aged 55 and above were estimated by multiplying the corresponding stage-specific

mammography sensitivities by the relative sensitivities of MRI (compared to mammography) derived from the MRISC study (with a maximum of 0.975). Stage-specific sensitivities of CBE in women aged 55 and above were based on a model evaluation of the Canadian National Breast Screening Study-2 (CNBSS-2) (17). We assumed CBE sensitivities for pre-menopausal women to be 50% of the CBE sensitivities for women aged 55 and above. For women aged 50-55 years, the sensitivities of the different screening tests were calculated by linear interpolation. Resulting values for sensitivity are shown in the Appendix table.

Duration

In MISCAN a higher tumor growth rate in younger women compared to older women is assumed (24). The age-specific mean durations of the screen-detectable preclinical stages were based on analysis of data from the Dutch nation-wide screening program (19). It has been shown that tumor growth rates of hereditary breast cancers decrease at increasing age (25). Resulting values for duration are shown in the Appendix table.

Improvement in prognosis

Up to now, the degree of improvement in prognosis after early detection in MISCAN had been based on the results of analyses of the five Swedish mammography screening trials (6). We re-estimated the stage-specific improvement in prognosis after screen detection, using updated long-term effects of the Swedish trials (3, 26, 27). We assumed this stage-specific benefit to be independent of the screening test used. Resulting values for improvement in prognosis are shown in the Appendix table.

Costs

All costs related to screening, assessment and treatment of breast cancer were taken into account (28). Costs of the different screening tests included medical staff, other personnel, disposables, fixed equipment and a mark-up for fixed costs and overheads (29). Both the cost of CBE and MRI were obtained from the Family Cancer Clinic of the Erasmus MC. The cost of CBE was based on actual time required for the first and follow-up CBE's, resulting in different cost estimates (€ 44 and € 17, respectively). Estimated cost of MRI was € 263, consisting of € 60 personnel cost, € 51 cost of disposables, € 84 cost of fixed equipment (including depreciation), and a mark-up of 35% (30). The cost of screening mammography (€ 49) was based on actual data on costs of the Dutch nation-wide breast cancer-screening program (23). The costs of assessment and treatment of breast cancer were obtained from previous studies (14, 28, 31), with a detailed overview elsewhere (14).

Cost-effectiveness analysis

MISCAN was used to predict costs and effects of various screening strategies for the three risk categories, with screening carried out during a period of 25 years. Costs and effects were computed over 100 years for a cohort of 1 million women aged 0-60 years with the age distribution (year 2000) obtained from Statistics Netherlands (32). An attendance rate of 90% at successive screening rounds was assumed. The costs were presented in European currency (€). The effects were presented in terms of steady-state breast cancer mortality reduction and number of life-years gained. Steady-state breast cancer mortality reduction was computed

from the mortality occurring in the last 10 years of the screening period (year 15-25). Cost-effectiveness ratios (CER) were expressed as cost per life-year gained, and incremental cost-effectiveness ratios (ICER) as additional cost per additional life-year gained. Costs and effects were discounted at a 3% annual discount rate (33). (I)CER's up to € 10,000 per (additional) life-year gained were considered as acceptable.

RESULTS

Comparison of MRISC study results with model predictions

Table 1 shows the number of diagnosed breast cancer cases, overall cumulative incidence rate and tumor characteristics as observed, and compares these with model predictions for the three risk categories. For *BRCA1/2* mutation carriers and the moderate-risk group, predicted breast cancer incidence corresponds quite closely to the observed incidence. Model predictions on age at diagnosis, tumor size and nodal status of breast cancers diagnosed in both risk groups were comparable with observed data, although observed age at diagnosis in *BRCA1/2* mutation carriers was somewhat younger than expected by the model. For the high-risk group, observed breast cancer incidence (15 per 1000 women) was clearly lower than the predicted incidence of 42 per 1000 women.

Effects and costs of screening women with increased risk for breast cancer with biannual CBE and annual mammography and MRI

For every risk group we calculated effects and costs of screening women aged 30-50 years with biannual CBE and annual mammography and MRI, followed by enrolment to the Dutch nation-wide screening program with biennial mammography for women aged 50-74 years (Table 2). Predicted (steady-state) breast cancer mortality reduction of screening women with increased breast cancer risk according to this regime varies from 39.5 to 40.9%, compared to 27.5% of screening women with average breast cancer risk in the Dutch biennial mammography screening program. Screening *BRCA1/2* mutation carriers with biannual CBE and annual mammography and MRI is predicted to be more cost-effective (CER of € 3,954 per life-year gained) than screening women with average breast cancer risk in the Dutch mammography screening program (CER of € 6,238 per life-year gained). Screening the high- and moderate-risk group with this regime is predicted to be less cost-effective.

Costs and effects of alternative screening policies for *BRCA1/2* mutation carriers

Table 3 presents predicted costs and effects of different screening regimes for *BRCA1/2* mutation carriers, varying in starting age, age of enrolment to the Dutch nation-wide mammography screening program, and screening intensity (interval and tests). Screening *BRCA1/2* mutation carriers with biennial mammography from age 50 to 74 years is a very cost-effective screening regime (CER of € 451 per life-year gained), however expected (steady-state) breast cancer mortality reduction is relatively low (18.7%). Biannual CBE and annual mammography and MRI up to age 60 (instead of age 50), after which enrolment to the Dutch mammography screening program takes place, leads to a reasonable ICER of € 6,466 per additional life-year gained and an expected (steady-state) breast cancer mortality reduction of 47.8%. Raising

Table 1. Comparison of observed number of breast cancer cases, overall cumulative incidence rate and tumor characteristics in the MRISC study, with model predictions, for three risk categories (50-85%, 30-50% and 15-30% CLTR*)

	Estimated 50-85% CLTR*		Estimated 30-50% CLTR*		Estimated 15-30% CLTR*	
	MRISC observation	Model expectation	MRISC observation	Model expectation	MRISC observation	Model expectation
Number of eligible women at entry	358		1052		499	
Woman-years at risk	867		2968		1414	
Number of screening tests						
Clinical breast examination	1397		4780		2250	
Mammography	773		2620		1222	
MRI	754		2437		1118	
Number of diagnosed breast cancer cases	23	24.9	16	44.6 †	11	10.5
Screen detected	19	19.9	15	36.1	11	8.4
Interval	4	5	1	8.5	0	2.1
Overall cumulative incidence rate (per 1000 women)	64	70	15	42 †	22	21
Cancer cases by age at diagnosis		†				
20-29 years	2	1.7	0	1.5	0	0.4
30-39 years	13	7.6	5	11.1	1	2.7
40-49 years	6	8.9	7	18.6	7	4.7
50-69 years	2	6.7	4	13.4	3	2.8
Cancer cases by tumor size						
DCIS	3	5	0	8.9	3	2
T1a / T1b (tumor ≤ 10 mm)	7	7.4	8	13.6	4	3.3
T1c (tumor 11-20 mm)	6	8.5	5	15.3	3	3.6
T2+ (tumor > 20 mm)	7	3.9	3	6.8	1	1.6
Cancer cases by nodal status						
N- / isolated cells	15	19.2	11	34.4	7	8.1
N+ / micrometastasis (0.2-2.0 mm)	4	5.7	4	10.2	1	2.4

* CLTR = Cumulative lifetime risk of developing breast cancer
† P-value ≤ 0.05

Table 2. Mortality effects, costs and cost-effectiveness indices of screening women with increased risk for breast cancer: biannual screening (CBE + mammography + MRI / CBE) for women aged 30-50 years, followed by biennial mammography for women aged 50-74 years. Comparison with the Dutch biennial mammography screening program for women with average breast cancer risk. 3% discount rate and costs in millions € (unless stated otherwise).*

	Biannual screening 30-50 years (CBE + mmg + MRI / CBE); biennial screening 50-74 years (mmg)			Dutch biennial mmg 50-74 years
	50-85% CLTR†	30-50% CLTR†	15-30% CLTR†	
	(compared to no screening)			
Deaths from breast cancer‡	-50,800	-27,900	-15,600	-3,700
Per year of screening‡	-2,032	-1,116	-624	-148
Breast cancer mortality reduction (steady-state)‡	40.9%	40.0%	39.5%	27.5%
Life-years lost from breast cancer (x 1,000)‡	-1,259	-681	-370	-55
Cost of screening	1,720	1,912	2,014	139
Costs of diagnostics of true positives (screened)	115	63	36	8
Costs of diagnostics of false positives (screened)	306	165	90	11
Cost of diagnostics outside the screening program	-51	-28	-15	-4
Cost of primary treatment	147	82	48	14
Cost of adjuvant treatment	4	2	2	1
Cost of follow-up	99	54	30	6
Cost of palliative care	-487	-268	-149	-34
Total cost	1,852	1,983	2,053	142
Deaths from breast cancer	-27,500	-15,100	-8,400	-1,900
Life-years lost from breast cancer (x 1,000)	-469	-254	-139	-23
Cost (€) per life-year gained (CE-ratio)	3,954	7,799	14,818	6,238

* Screening is carried out during a period of 25 years. Costs and effects are computed over 100 years, for a cohort of 1 million women aged 0-60 years.
† CLTR = Cumulative lifetime risk of developing breast cancer.
‡ Not discounted.

the upper age limit of intensive screening from 60 to 74 years or lowering the lower age limit from 30 to 25 years results in somewhat more favorable breast cancer mortality reductions (50.2% and 49.4% respectively), however the incremental cost per additional life-year gained is relatively high.

Screening *BRCA1/2* mutation carriers from age 30 to 60 years according to the now generally applied guidelines (biannual CBE and annual mammography) (34) is expected to lead to 40.7% (steady-state) breast cancer mortality reduction. Replacing mammography by MRI, or adding annual MRI to this screening regime, will lead to a (steady-state) breast cancer mortality reduction of 45.8% and 47.8% respectively.

Table 3. Alternative screening policies for *BRCA 1/2* mutation carriers (50-85% cumulative lifetime risk for developing breast cancer), estimated by MISCAN*. Policies characterized by age range, screening interval and screening tests of intensive screening, and age of enrolment to the Dutch nation-wide mammography screening program, and expressed as total cost and effects, the cost-effectiveness ratio (CER), and the incremental cost effectiveness ratio (ICER). 3% discount rate and costs in € (unless stated otherwise).†

	Age range of intensive screening (years)	Age of enrolment to Dutch biennial mmg (until age 74)	Screening interval of intensive screening (years)	Screening tests of intensive screening	Costs	Effects	Effects	CER	ICER‡	ICER§
					Total cost (x 1,000000)	Breast cancer mortality reduction (steady-state)‖	Life-years gained (x 1,000)	Costs per life-year gained	Costs per life-year gained	Costs per life-year gained
					(compared to no screening)					
	---	50	---	---	68	18.7%	151	451	---	---
Upper age limit	30-50	50	0.5	CBE + mmg + MRI / CBE¶	1,852	40.9%	469	3,954	5,610	---
	30-60	60	0.5	CBE + mmg + MRI / CBE	2,360	47.8%	547	4,314		6,466
	30-74	---	0.5	CBE + mmg + MRI / CBE	2,647	50.2%	562	4,711		19,349
Lower age limit	35-60	60	0.5	CBE + mmg + MRI / CBE	1,919	44.8%	498	3,853	5,334	---
	30-60	60	0.5	CBE + mmg + MRI / CBE	2,360	47.8%	547	4,314		9,026
	25-60	60	0.5	CBE + mmg + MRI / CBE	2,779	49.4%	578	4,812		13,742
Less / equally intensive	30-60	60	0.5	CBE + mmg / CBE (guideline)	687	40.7%	451	1,523	2,063	---
	30-60	60	0.5	CBE + MRI / CBE	2,026	45.8%	526	3,853		17,849 (compared to guideline)
	30-60	60	0.5	CBE + mmg + MRI / CBE	2,360	47.8%	547	4,314		17,400 (compared to guideline)
	30-60	60	1	CBE + mmg + MRI	2,252	45.7%	527	4,276		20,595 (compared to guideline)
	30-60	60	0.5	CBE + MRI / CBE + mmg	2,363	50.1%	574	4,117		13,622 (compared to guideline)
Alternative: less CBE	30-60	60	0.5	MRI / mmg	2,135	48.5%	556	3,841	5,113	---
	30-60	60	0.5	MRI / CBE + mmg	2,258	49.3%	569	3,972		9,705
	30-60	60	0.5	CBE + MRI / CBE + mmg	2,363	50.1%	574	4,117		18,252
Alternative: more MRI	30-60	60	0.5	MRI / CBE + mmg	2,258	49.3%	569	3,972	5,253	---
	30-60	60	0.5	CBE + mmg + MRI / MRI	3,877	53.1%	622	6,236		29,992
	30-60	60	0.5	CBE + mmg + MRI / CBE + MRI	3,979	53.3%	625	6,372		36,881

* MISCAN = MIcrosimulation SCreening ANalysis.
† Screening is carried out during a period of 25 years. Costs and effects are computed over 100 years, for a cohort of 1 million women aged 0-60 years.
‡ The incremental cost-effectiveness ratio is calculated by dividing the difference in costs between biennial mammography from age 50 to 74 years with the current screening policy by the difference in effects between these screening policies.
§ The incremental cost-effectiveness ratio is calculated by dividing the difference in costs between the previous screening policy with the current screening policy by the difference in effects between these screening policies.
‖ Not discounted.
¶ CBE = clinical breast examination; mmg = mammography; MRI = magnetic resonance imaging.

Table 4. Alternative screening policies for the moderate-risk category (15-30% cumulative lifetime risk for developing breast cancer), estimated by MISCAN*. Policies characterized by age range, screening interval and screening tests of intensive screening, and age of enrolment to the Dutch nation-wide mammography screening program, and expressed as total cost and effects, the cost-effectiveness ratio (CER), and the incremental cost effectiveness ratio (ICER). 3% discount rate and costs in € (unless stated otherwise).†

	Age range of intensive screening (years)	Age of enrolment to Dutch biennial mmg (until age 74)	Screening interval of intensive screening (years)	Screening tests of intensive screening	Costs	Effects	Effects	CER	ICER‡	ICER§
					Total cost (x 1,000000)	Breast cancer mortality reduction (steady-state)‖	Life-years gained (x 1,000)	Costs per life-year gained	Costs per life-year gained	Costs per life-year gained
					(compared to no screening)					
	---	50	---	---	129	20.4%	47	2,727	---	---
Upper age limit	30-50	50	0.5	MRI / CBE + mmg¶	1,964	39.7%	143	13,745	19,115	---
	30-55	55	0.5	MRI / CBE + mmg	2,363	44.2%	159	14,836		24,342
	30-60	60	0.5	MRI / CBE + mmg	2,729	47.2%	169	16,176		38,808
Lower age limit	40-50	50	0.5	MRI / CBE + mmg	1,083	33.8%	109	9,931	15,387	---
	35-50	50	0.5	MRI / CBE + mmg	1,538	37.4%	129	11,960		23,293
	30-50	50	0.5	MRI / CBE + mmg	1,964	39.7%	143	13,745		29,865
Longer screening interval	40-50	50	2	MRI / CBE + mmg	410	26.9%	78	5,264	9,065	---
	40-50	50	1.5	MRI / CBE + mmg	507	28.2%	84	6,039		16,182
	40-50	50	1	MRI / CBE + mmg	620	30.2%	93	6,681		12,745
	40-50	50	0.5	MRI / CBE + mmg	1,083	33.8%	109	9,931		28,445
Alternative: only mmg	40-50	50	2	mmg	209	24.5%	68	3,080	3,810	---
	40-50	50	1.5	mmg	243	25.6%	73	3,332		6,797
	40-50	50	1	mmg	291	27.3%	79	3,702		8,304
	40-50	50	0.5	mmg	447	30.7%	94	4,764		10,225
	35-50	50	0.5	mmg	598	33.5%	109	5,460		9,669
	30-50	50	0.5	mmg	738	34.9%	119	6,224		15,446
Alternative: mmg + CBE	40-50	50	1	mmg	291	27.3%	79	3,702	5,063	---
	40-50	50	0.5	mmg / CBE	358	29.2%	87	4,126		8,225
	40-50	50	0.5	CBE + mmg / CBE (guideline)	405	30.0%	92	4,418		9,488
	40-50	50	0.5	mmg	447	30.7%	94	4,764		19,467
Alternative: mmg + CBE	40-50	50	2	mmg	209	24.5%	68	3,080	3,810	---
	40-50	50	1	mmg / CBE	253	25.9%	73	3,485		9,317
	40-50	50	1	CBE + mmg / CBE	276	26.9%	77	3,573		4,907
	40-50	50	1	mmg	291	27.3%	79	3,702		11,400

* MISCAN = MIcrosimulation SCreening ANalysis.
† Screening is carried out during a period of 25 years. Costs and effects are computed over 100 years, for a cohort of 1 million women aged 0-60 years.
‡ The incremental cost-effectiveness ratio is calculated by dividing the difference in costs between biennial mammography from age 50 to 74 years with the current screening policy by the difference in effects between these screening policies.
§ The incremental cost-effectiveness ratio is calculated by dividing the difference in costs between the previous screening policy with the current screening policy by the difference in effects between these screening policies.
‖ Not discounted.
¶ CBE = clinical breast examination; mmg = mammography; MRI = magnetic resonance imaging.

From the viewpoint of cost-effectiveness, it can be considered to offer MRI and mammography at different time points: biannual screening with CBE and MRI (visit A) and CBE and mammography (visit B) is estimated to gain more life-years (50.1% breast cancer mortality reduction) at the same cost, compared to biannual screening with CBE, mammography and MRI (visit A) and CBE (visit B). Furthermore, offering biannual screening with MRI (visit A) and CBE and mammography (visit B) is even more preferable: the incremental cost of adding a CBE to MRI is relatively high (€ 18,252 per additional life-year gained).

Costs and effects of alternative screening policies for the moderate-risk category

The preferable screening regime for *BRCA1/2* mutation carriers, biannual screening with MRI (visit A) and CBE and mammography (visit B) from age 30 to 60, results in a four times higher CER if applied to the moderate-risk category, mostly due to less life-years gained because of a lower breast cancer incidence rate. Table 4 shows this screening policy varying in age range and screening interval. Lowering the upper age limit or raising the lower age limit still results in CER's above € 10,000 per life-year gained. This screening regime is most cost-effective for women aged 40-50 with a two-year interval, with an ICER of € 9,065 per additional life-year gained compared to biennial mammography from age 50 to 74 years.

However, screening regimes with only mammography, alternatively in combination with CBE, are more favorable in terms of cost-effectiveness (Table 4): annual mammography for women aged 40-50 years, after which enrolment to the Dutch mammography screening program takes place, will gain the same amount of life-years at lower cost, compared to biennial screening with MRI (visit A) and CBE and mammography (visit B). Screening women aged 40-50 years according to the now generally applied guidelines (biannual CBE and annual mammography) (34) leads to an expected (steady-state) breast cancer mortality reduction of 30.0%, and is preferable to biannual mammography: the incremental cost of replacing both CBE's by an additional mammography is € 19,467 per additional life-year gained.

DISCUSSION

This study estimates that screening women with increased breast cancer risk with biannual CBE and annual mammography and MRI is predicted to be one and a half times more effective compared to a biennial mammography screening program for women with average breast cancer risk. The assumption is that the larger stage-shift is reflected in a proportionally larger breast cancer mortality reduction than observed in randomized mammography screening trials. Screening *BRCA1/2* mutation carriers according to this regime is even more cost-effective, although it can be considered to offer MRI and mammography at different time points (50.1% breast cancer mortality reduction). For *BRCA1/2* mutation carriers, biannual screening with MRI (visit A) and CBE and mammography (visit B) from age 30 to 60 years is preferable from a cost-effectiveness viewpoint. For the moderate-risk category, screening regimes with only mammography, alternatively in combination with CBE, in women aged 40-50 years are most cost-effective.

Besides intensive surveillance, prophylactic mastectomy is an alternative risk reducing strategy, especially for *BRCA1/2* mutation carriers (35, 36). In the Family Cancer Clinic of the

Erasmus MC, approximately half of the unaffected *BRCA1/2* mutation carriers opts for prophylactic mastectomy (37). However, the use and accessibility of prophylactic surgery differs largely between countries (38). Although the risk of dying from breast cancer may be reduced by almost 100%, the physical and psychological morbidity of risk-reducing surgery may be unacceptable for some women. Our results may indicate that intensive surveillance is an effective alternative to reduce the risk of breast cancer death by 50%.

Observed breast cancer incidence in the high-risk group was clearly lower than we predicted, especially above age 40, and was also lower than the observed incidence in the moderate-risk category (9). Assuming a lifetime background risk of developing breast cancer of 15-30% (model risk of 22.5%) for both the high- and moderate-risk group, resulted in a better fit of predicted breast cancer incidence with observed incidence for both risk categories taken together. We therefore did not calculate the effectiveness and cost-effectiveness of alternative screening policies for the high-risk group. Our threshold of 30% CLTR between the moderate- and high-risk category is arbitrary, and may have caused shifting of breast cancer incidence to the moderate-risk category. Also, women's CLTR may have been overestimated (e.g. the posterior risk of *BRCA1/2* carriership decreases with age; DNA-testing excluded *BRCA1/2* in the family) or underestimated (e.g. additional breast and/or ovarian cancer cases after the closing date of the study; small family size). Finally, the actual age-related penetrance in the high-risk group may be different from the one assumed by Claus et al. (15). Besides longer study follow-up, more research on the risk assessment and risk categorization of women in the high-risk group is warranted to explain the observed results, and to advise a screening regime for this risk category.

Comparison of cost-effectiveness studies in breast cancer screening between different countries reveals a wide range of cost-effectiveness outcomes from comparable studies. The cost per life-year gained of routine mammographic screening in the United States seems to be about four-fold the cost per life-year gained in the Netherlands (39). A substantial part of this difference is due to actual differences in the pricing of health care services as well as different medical practice patterns. Therefore, cost-effectiveness ratios of screening women with increased breast cancer risk in the United States will probably be four times the current reported results for the Netherlands. However, this will not influence the comparison between different screening alternatives, unless the ratio between the costs of MRI and mammography is different for the United States or other countries.

Stage-specific sensitivities of CBE in women aged 55 and above were based on a model evaluation of the CNBSS-2, and were quite high (17) (Appendix table). It is known that CBE in the CNBSS-2 was performed well. In that study CBE included both visual examination and palpation, and was primarily performed by specially trained nurse-examiners, who were closely monitored during the study (40, 41). Overall CBE sensitivity in the MRISC study was lower (9). However, we did not use stage-specific CBE sensitivities derived from the MRISC study because of the small number of cancers detected in the various stages.

From a cost-effectiveness viewpoint, intensive surveillance without MRI is defendable for the moderate-risk category. However, MRI may be of additional clinical significance in specific subgroups, like younger women with very dense glandular breast tissue.

Because there is a constraint on the total amount of resources that are available for health care, costs and benefits of any particular health care intervention have to be compared to

alternative interventions. Here, the cost-effectiveness ratios of most screening variants stayed within the limit of € 10,000 per life-year gained. For other prevention programs cost-effectiveness ratios of € 10,000 to € 14,000 have been accepted in the Netherlands (42, 43). In a study on the cost-effectiveness of five-hundred life-saving interventions in the United States, the median medical intervention cost was $ 19,000 per life-year gained (44).

The risk of inducing breast cancer deaths through radiation exposure in women having mammography was not taken into account. This risk has been shown to be dependent on age at exposure, time since exposure and the total accumulated dose (45-47). The balance between the number of breast cancer deaths induced by radiation and those prevented by early detection through mammography is significantly more unfavorable for women under age 50 (48).

When offering MRI and mammography at different time points, MRI might be used as additional diagnostic investigation when results of mammography screening are uncertain or suspicious. We did not take into account the extra costs of diagnostic MRI. More research is warranted on the use of MRI as additional diagnostic evaluation after mammography screening in women with increased breast cancer risk.

Costs and effects were calculated for a hypothetical cohort of 1 million women aged 0-60 years. In practice, CER's will be less favorable due to smaller scale size. We estimated the number of women with increased breast cancer risk to be 2.5% of the total female population (49), with 0.35% being *BRCA1/2* mutation carriers (50) and 2.15% being equally spread over the high- and moderate-risk category.

Our present model analysis is based on the numbers of breast cancers detected in the various risk categories of the MRISC study, which are relatively small because of limited follow-up time (median 2.9 years). With longer follow-up the model parameters on screening sensitivity and specificity may be adjusted, and re-estimation of the costs and effects of various screening regimes for the different risk groups is advisable.

Although there may be some uncertainty in predictions made by modeling, there is no alternative way to investigate the effectiveness of MRI screening in women with increased breast cancer risk. A randomized controlled trial in these women would have been practically impossible. However, our model results on the performance of screening have been compatible with the results of mammography screening trials in women with average breast cancer risk (6, 17, 20, 51).

In conclusion, our study estimates that including MRI in *BRCA1/2* mutation carriers surveillance is a very cost-effective screening policy, and should therefore be offered in countries with a nation-wide screening program for average risk women. Given the estimated breast cancer mortality reduction it is one of the first times that an effective alternative to prophylactic mastectomy is proposed. For the moderate-risk category, MRI is unlikely to be cost-effective, and screening regimes with only mammography, alternatively in combination with CBE, may well lead to substantial breast cancer mortality reductions. For the high-risk group, longer study follow-up or pooling with data from other studies is needed.

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Appendix table. Values for sensitivity, duration and improvement in prognosis as used in the MISCAN model

Sensitivity of different screening tests by stage and age (clinical breast examination / mammography / MRI)*

Stage	*Age < 50 years*	*Age > 55 years*
Preclinical DCIS	0.027 / 0.200 / 0.080	0.053 / 0.400 / 0.080
Preclinical T1a (tumor ≤ 5 mm)	0.004 / 0.140 / 0.778	0.008 / 0.650 / 0.975
Preclinical T1b (tumor 6-10 mm)	0.079 / 0.180 / 0.778	0.158 / 0.800 / 0.975
Preclinical T1c (tumor 11-20 mm)	0.239 / 0.450 / 0.810	0.478 / 0.900 / 0.975
Preclinical T2+ (tumor > 20 mm)	0.325 / 0.500 / 0.810	0.649 / 0.950 / 0.975

Mean duration (years) of screen-detectable preclinical stage by age

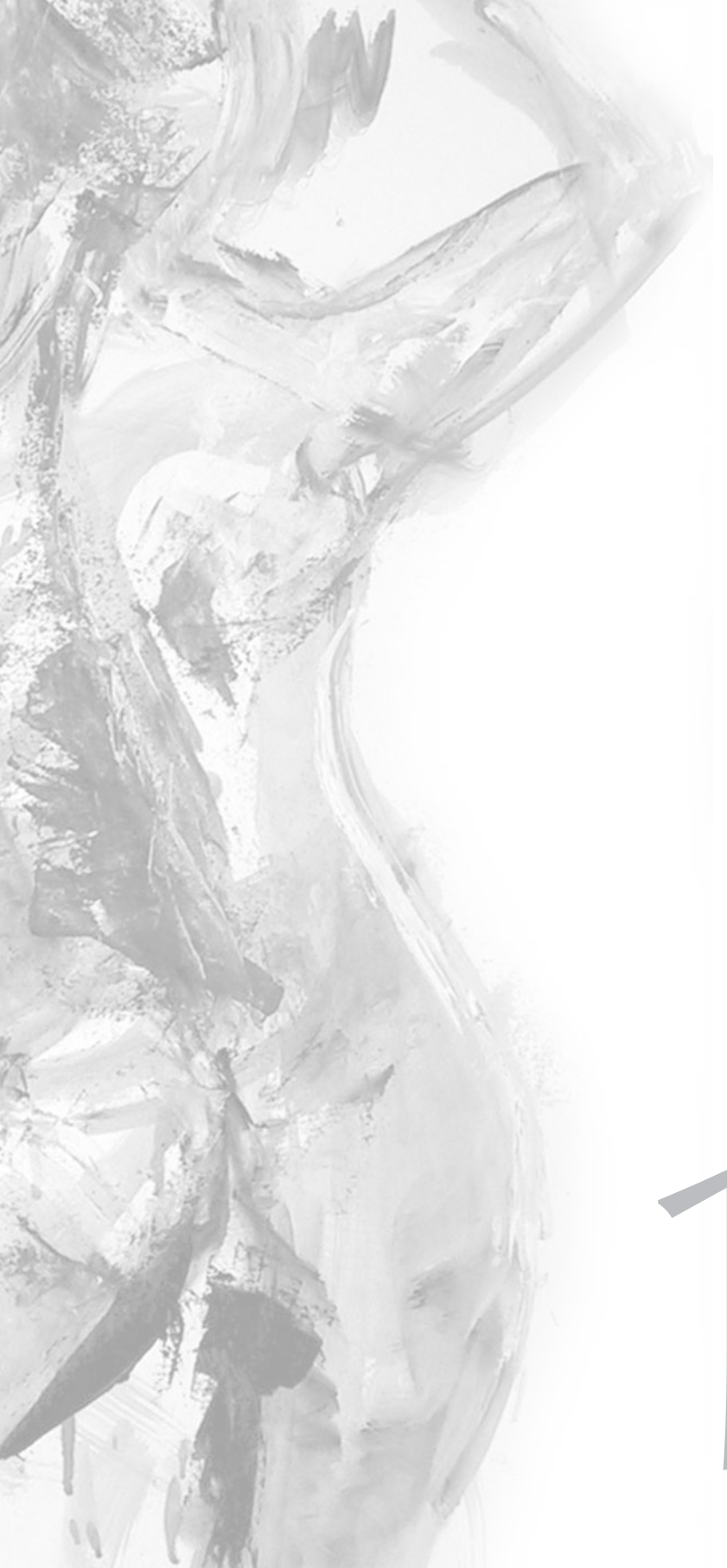
Stage	*Age 30*	*Age 40*	*Age 50*	*Age 60*	*Age 70*
Preclinical DCIS	5.22	5.22	5.22	5.22	5.22
Preclinical T1a (tumor ≤ 5 mm)	0.06	0.07	0.10	0.14	0.18
Preclinical T1b (tumor 6-10 mm)	0.28	0.37	0.50	0.72	0.89
Preclinical T1c (tumor 11-20 mm)	0.58	0.76	1.03	1.49	1.84
Preclinical T2+ (tumor > 20 mm)	0.44	0.57	0.77	1.12	1.38

Reduction in risk of dying of breast cancer by stage in which (pre)cancer is detected (at age 40-49)†

	Reduction in risk	
Stage	*N-*	*N+*
Preclinical DCIS	100%	100%
Preclinical T1a (tumor ≤ 5 mm)	89.9%	76.9%
Preclinical T1b (tumor 6-10 mm)	86.8%	70.6%
Preclinical T1c (tumor 11-20 mm)	79.7%	57.0%
Preclinical T2+ (tumor > 20 mm)	63.4%	32.5%

* Sensitivity between ages 50 en 55 years is calculated by linear interpolation

† In the MISCAN model, the probability of cure is equal to the probability of long-term relative survival



Discussion

10

INTRODUCTION

In this chapter, the two research questions as formulated in Chapter 1 are answered. Subsequently, additional aspects of screening women with a familial or genetic predisposition to breast cancer are discussed, and suggestions for future research are given. The chapter ends with several general conclusions and recommendations resulting from the work presented in this thesis.

ANSWERING THE RESEARCH QUESTIONS

Research question 1: *What are the quality of life and psychological effects of the screening process in screening women with a familial or genetic predisposition to breast cancer?*

Answer: *Screening for breast cancer in women with a familial or genetic predisposition does not have an adverse effect on health-related quality of life and general distress.*

Comment: No studies had been performed before to investigate the short-term effects of intensive screening on health-related quality of life in women at increased risk for breast cancer due to a familial or genetic predisposition. Chapter 4 showed that screening these women by biannual CBE and annual mammography and MRI, did not have a relevant impact on generic health-related quality of life. The results also did not provide evidence for a general distress-raising effect of screening. MRI was acceptable as a screening modality for these women, and was preferred over mammography (chapter 6).

Interestingly, it appeared that the study population showed significantly better generic health-related quality of life scores as compared to the age-/sex-adjusted reference scores. It may seem that women with increased breast cancer risk who choose for intensive screening have a better health status than women from the general population. Most of the women opt for intensive screening voluntarily, and this may result in a selection of healthy and well-coping women. The difference in health status may partly be due to observed difference in educational level between the study sample and the general population.

The impact of the screening process on general distress was measured by empirical assessment at various stages in the screening process, using the somatic subscale of the Symptom Checklist-90 and the role-emotional and mental health scale of the SF-36, which may be too general. The use of a specific measure of psychological consequences of breast cancer screening, like the PCQ, could provide additional insight. Meanwhile, the PCQ has been translated successfully into Dutch, and seems useful in measuring psychological morbidity among women under regular surveillance because of increased breast cancer risk (chapter 2). Additional insight in the psychological impact of breast cancer screening in these women, using results of the PCQ, may be provided in the near future.

Two subgroups showed elevated levels of general and/or breast cancer-specific distress at baseline of the study, i.e. two months prior to the scheduled screening visit. Women with a higher affective risk perception (23% of the study population had an affective risk perception varying from high to very high) showed higher scores for general and breast cancer-specific

distress (regardless of accurate cognitive risk estimation, overestimation or underestimation) (chapter 3). Higher breast cancer-specific distress scores were also observed among younger women who examined their breasts at least once a week (7% of the study population), while monthly breast self-examination (BSE) is recommended (chapter 5).

Research question 2: *What are the breast cancer mortality effects and cost-effectiveness of various screening policies, including MRI, for women with a familial or genetic predisposition to breast cancer?*

Answer: *Screening women with increased breast cancer risk with biannual clinical breast examination (CBE) and annual mammography and MRI is estimated to lead to 40% (steady-state) breast cancer mortality reduction. Including MRI in BRCA1/2 mutation carriers (50-85% cumulative lifetime risk (CLTR)) surveillance is cost-effective. For the moderate-risk category (15-30% CLTR), MRI screening is unlikely to be cost-effective. For the high-risk group (30-50% CLTR) we were unable to draw firm conclusions for or against including MRI in screening.*

Comment: Chapter 9 showed that intensive surveillance including MRI in *BRCA1/2* mutation carriers is estimated to reduce breast cancer mortality by 50.1%, compared to 40.7% by mammography and CBE only. Its effectiveness is almost twice as high compared to mammography screening in women with average risk. Screening *BRCA1/2* mutation carriers with biannual CBE and annual mammography and MRI from age 30 to 60 is at a cost of € 4,314 per life-year gained (3% discounting). Offering MRI and mammography alternately at a 6 months interval is even more cost-effective (€ 4,117 per life-year gained). For the moderate-risk category, screening regimes with only mammography, alternatively in combination with CBE, from age 40 to 50 years are most favourable in terms of cost-effectiveness (range € 3,080 - € 4,764), and may lead to 24.5-30.7% breast cancer mortality reduction.

Long-term effectiveness in terms of breast cancer mortality reduction of screening women with increased breast cancer risk is still unknown from ongoing studies. Therefore the MISCAN breast cancer-screening model, which has been successfully applied in the evaluation of different cancer-screening programmes (1-3), was used to predict effectiveness and cost-effectiveness of various screening policies for these women. With screening data from the MRISC study we estimated stage-specific sensitivity of different screening tests and resulting stage-shift by screen detection, which were incorporated into the model. The benefit of this stage-shift, i.e. improvement in prognosis after screen detection, was validated on results of the Swedish randomised mammography screening trials (4-6). The benefit of early detection by mammography in the average female population was applied to early detection by CBE, mammography or MRI in women with increased breast cancer risk.

Contrary to the Swedish mammography trials, the Canadian National Breast Screening Study (CNBSS-2) was designed to compare breast cancer mortality between a control arm screened annually by CBE and a study arm screened by CBE and mammography. Because of this design, no estimations of mammography benefit compared to no screening could be made. We therefore performed a model evaluation of this trial: an estimated breast cancer mortality reduction by mammography screening compared to no screening for women aged

50-59 in the CNBSS-2 of at least 13.6% seems plausible (chapter 7). This result can be judged as compatible with the results of the other trials of mammography screening, and we therefore had no reason to adjust the improvement in prognosis after screen detection as used in the MISCAN model.

The model analysis was based on the numbers of breast cancers detected in the various risk categories of the MRISC study, which are relatively small because of limited follow-up time. With results from longer follow-up, the model parameters on screening sensitivity and specificity can be adjusted, and costs and effects of various screening regimes for the different risk groups can be re-estimated.

Stage-specific sensitivities of CBE in women aged 55 and above were based on the model evaluation of the CNBSS-2 (chapter 7): estimated sensitivities varied from 0.29 to 0.48 for stage T1c and from 0.60 to 0.65 for stage T2+. An explanation for these high sensitivities is that CBE in the CNBSS included both inspection and palpation, and was primarily performed by specially trained nurse-examiners, who were moreover closely monitored during the study. Stage-standardized CBE sensitivity in the MRISC study was 0.18, which was lower than estimated stage-standardized CBE sensitivity in the CNBSS-2 (varying from 0.35 to 0.48) (the observed stage-distribution of screen-detected cancers in the control arm of the CNBSS-2 was used as standard). We did not use stage-specific CBE sensitivities derived from the MRISC study because of the small number of cancers detected in the various stages.

ADDITIONAL ASPECTS OF SCREENING WOMEN WITH A FAMILIAL OR GENETIC PREDISPOSITION TO BREAST CANCER

Radiation induced breast cancer by mammography screening

Mortality effects and cost-effectiveness of various screening policies (chapter 9) did not include an estimation of the number of breast cancer deaths induced by radiation exposure in women having mammography. Studies of radiation-exposed women have consistently shown that the female breast is susceptible to the carcinogenic effects of ionising radiation. Information on breast cancer risks and radiation mainly comes from epidemiological studies of atomic bomb survivors (7, 8) or women exposed to relatively high doses of radiation for diagnostic (9, 10) or therapeutic reasons (11-13). These studies have shown that the risk of inducing breast cancer (death) is dependent on age at exposure, time since exposure and the total accumulated dose.

In mammography screening, women are exposed to very low doses of radiation. Since the studies on the effects of low dose radiation that have so far been carried out are not yet conclusive (14, 15), risk estimates of inducing breast cancer (death) by mammography have to be deduced from analyses of the various epidemiological studies on high-dose radiation effects. For example, the US committee on the Biological Effects of Ionising Radiations (BEIR-V) has adopted a risk model derived from epidemiological data (16), which can be used to estimate the risk of dying from breast cancer due to low dose mammography.

In the Dutch nation-wide breast cancer screening programme, more than 1 million women (50-74 years) are invited for screening per year (17). Screening consists of a two-view mam-

mography at first screening and a one-view mammography at subsequent screenings, with an interval of two years. Until recently, the average dose per view was assumed to be 2 mGy. Estimates of the number of breast cancer deaths induced in the Dutch mammography screening programme have been made, using the BEIR-V model (18). The number of deaths induced versus those prevented was estimated to be 1:242, which means that radiation induced breast cancer deaths form a relatively minor problem. Moreover, some deaths from radiation induced breast cancer will be prevented by early detection of these tumours in the same screening programme. When this is taken into account, an even better ratio of induced vs. prevented deaths of 1:294 results.

Women with increased risk for breast cancer due to a familial or genetic predisposition are often diagnosed before the age of 50 (19, 20). Results from chapter 9 lead to a recommendation to start screening these women at age 30 or 40 years, depending on the CLTR of developing breast cancer. Since breast tissue is more sensitive to radiation in younger women and younger women have a longer life expectancy, an important determinant of radiation risk in breast cancer screening is age of screening (18). The relationship between the risk of breast-cancer deaths induced by radiation and age at exposure, based on the BEIR-V model and the Dutch demography and mortality from breast cancer, is shown in Figure 1. Results on the number of deaths induced versus those prevented in the Dutch mammography screening programme became less favourable when screening was extended to women aged 40-49 (1:97). An even less favourable balance will probably apply for screening women under age 40.

Another determinant of radiation risk in breast cancer screening is screening interval (18). For women with increased breast cancer risk, annual mammography is advised until age 50 or 60 (chapter 9), depending on the CLTR of developing breast cancer, followed by enrolment

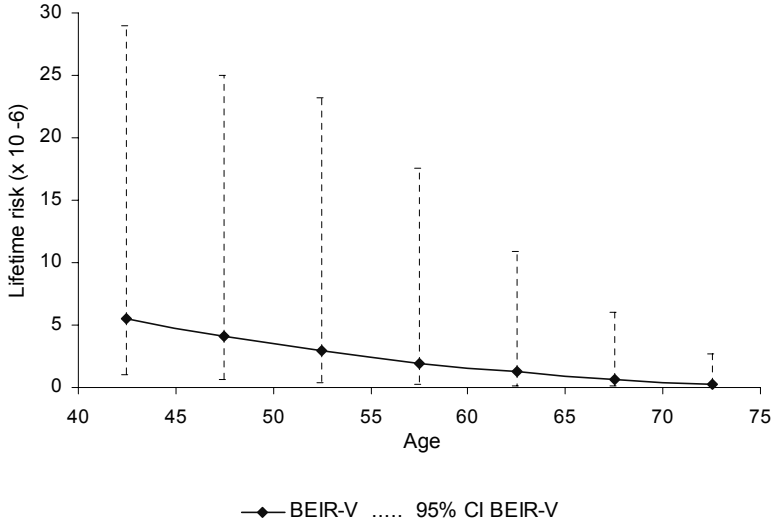


Figure 1. Expected lifetime risk of radiation induced breast cancer death by age at exposure, for women exposed once to 1 mGy (95% Credibility Intervals), BEIR-V (16)

to a biennial mammography screening programme. Screening all women aged 40-69 in the Dutch mammography screening programme with a 1-year interval, would lead to a less favourable ratio of number of deaths induced versus those prevented of 1:73.

Presented results are based on an average dose per view of 2 mGy in the Dutch mammography screening programme. Only recently, the average dose per view was estimated to be 1.3 mGy (21). In the BEIR-V model, the risk of radiation is proportional to the dose. Consequently, the estimated number of breast cancer deaths induced in the Dutch mammography screening programme will be reduced with 35%. Since radiation dose varies depending on age of the woman, breast density and breast size (22, 23), it is possible that higher radiation doses are used in women with increased breast cancer risk, because of younger age and denser breast tissue. Higher radiation doses in women under age 50 were not taken into account in presented results.

Of special interest is the question whether *BRCA1/2* mutation carriers are at increased risk of radiation associated breast cancer compared to women who do not carry such a mutation. Women susceptible to breast cancer due to a genetic mutation seem to be at an increased risk of radiation-induced DNA damage (24). Several studies suggest that tumour induction is strongly related to being a mutation carrier (25-29). New results from the International *BRCA1/2* Carrier Cohort Study (IBCCS) show that *BRCA1/2* carriers exposed to chest X-rays had a significantly increased risk of breast cancer compared to those reporting no chest X-rays. Estimated risk was higher in carrier women aged 40 and younger, and was highest in carrier women exposed to X-rays before age 20 only (30).

In the near future, estimations of the number of breast cancer deaths induced by mammography screening should be made specifically for women with a familial or genetic predisposition to breast cancer, using for example the BEIR-V model, and presented mortality effects and cost-effectiveness of various screening policies may be adjusted.

Risk assessment in the high-risk group (30-50% CLTR)

The effectiveness and cost-effectiveness of alternative screening policies for the high-risk category (30-50% CLTR) were not calculated: breast cancer incidence in the high-risk group of the MRISC study was much lower than predicted (chapter 9), and was even lower than the incidence in the moderate-risk category (15-30% CLTR) (31).

In the MRISC study, lifetime risk categories for breast cancer were based on modified tables of Claus (32, 33), with risk of developing breast cancer dependent on the number of family members with breast cancer (1, 2 or ≥ 3), their age at diagnosis, whether they were first- or second-degree relatives, and family history of ovarian cancer. The lifetime risk categories for breast cancer are indicated in Table 1.

The threshold of 30% CLTR between the moderate- and high-risk category as used in the MRISC study is arbitrary, and may have caused shifting of breast cancer incidence to the moderate-risk category. Also, CLTR of developing breast cancer may have been overestimated in women with a 50% risk of *BRCA1/2* mutation carriership (high-risk category, Table 1):

- Women with a 50% risk of *BRCA1/2* mutation carriership have a theoretical chance of 50% to have a mutation in the *BRCA1* or *BRCA2* gene. However, the actual chance of being a *BRCA1/2* mutation carrier may be lower for relatively older women who did not had breast

Table 1. Risk stratification to determine the cumulative lifetime risk for breast cancer

BRCA1/2 mutation carriers (cumulative lifetime risk 50-85%) 1. Proven or obligate mutation carriers
High-risk (cumulative lifetime risk 30-50%). Women with: 1. A first-degree family member with a *BRCA1/2* mutation (50% risk of *BRCA1/2* mutation carriership) 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
Moderate-risk (cumulative lifetime risk 15-30%). Women with: 1. A second-degree family member with a *BRCA1/2* mutation (25% risk of *BRCA1/2* mutation carriership) 2. One first-degree family member with breast cancer younger than 40 years 3. Two first-degree or one first- and one second-degree family members with breast cancer, mean age at diagnosis between 45 and 60 years 4. Three second-degree family members with breast or ovarian cancer 5. Two first-degree or one first and one second-degree family members, one affected with breast cancer younger than 55 and one with ovarian cancer

cancer yet. Taking into account this lower actual chance could lead to a lower CLTR of developing breast cancer.

- There is a stochastic chance that the women with a 50% risk of *BRCA1/2* mutation carriership are mainly women without a *BRCA1/2* mutation. These women have an average lifetime risk of developing breast cancer of 8-10%.
- Part of the women with a 50% risk of *BRCA1/2* mutation carriership opted for genetic testing during the MRISC study themselves. However, for administrative reasons it is possible that these women were still registered in the high-risk category, although DNA-testing excluded a *BRCA1/2* mutation in some women.

Finally, the actual age-related penetrance in the high-risk group may be different from the one assumed by Claus et al. (32). More research on the risk assessment and risk categorisation of women in the high-risk group is warranted to explain the observed results. Besides, longer study follow-up or pooling with data from other studies is needed to advise a screening regime for this risk category.

Alternation of mammography and MRI screening

From the viewpoint of cost-effectiveness, it seems advisable to offer mammography and MRI alternately at a 6 months interval, especially in screening *BRCA1/2* mutation carriers (chapter 9). However, when mammography and MRI screening is alternated, MRI might be used as additional follow-up when results of mammography screening are uncertain or suspicious. In our cost-effectiveness calculations we did not take into account the possible extra costs and extra benefits of follow-up MRI.

A pilot study of alternation of mammography and MRI in screening *BRCA1/2* mutation carriers could give insight in the use of follow-up by MRI, ultrasonography, fine-needle as-

piration and biopsy. Cost-effectiveness of offering mammography and MRI alternately at a 6 months interval could be re-estimated, using this information. Starting a new screening study to investigate the effectiveness and cost-effectiveness of alternation might be recommendable, although this will take longer follow-up time and extra costs.

CBE screening in women with a familial or genetic predisposition to breast cancer

Besides the efficacy of MRI compared to mammography in screening women with increased breast cancer risk, the MRISC study also investigated the screening performance of CBE in these women: overall sensitivity of CBE was 17.8% and specificity was 98.1% (31). A Canadian study compared the sensitivity and specificity of four methods of breast cancer surveillance (MRI, mammography, ultrasound and CBE) in *BRCA1/2* mutation carriers (34). In that study, sensitivity of CBE was 9.1% and specificity was 99.3%; a benefit from CBE over and above the combination of the 3 imaging modalities was not observed. Comparison of mammography, ultrasound and CBE in screening female relatives of breast cancer patients in Taiwan resulted in an overall CBE sensitivity of 33.3% and a specificity of 83.5% (35).

Estimated stage-specific CBE sensitivities in the CNBSS-2 were quite high (chapter 7). Women enrolled in that study had above average risk: estimated breast cancer incidence rate in the trial population was higher than the average Canadian rate (relative increase of 24-29%) (chapter 7). However, it is unknown whether some of these women had a familial or genetic predisposition to breast cancer. High CBE sensitivities for larger tumours might be plausible with the intensive type of screening as performed in the CNBSS-2, although the quality of CBE in a community setting is likely to be lower (36, 37). Despite high CBE sensitivities derived from the CNBSS-2 results, which were used in our cost-effectiveness calculations, the additional effectiveness of adding a CBE to MRI screening seems low in women with increased breast cancer risk, leading to relatively high incremental cost (chapter 9).

These opposite results give rise to the question whether it is justified to use CBE as a screening modality for women with a familial or genetic predisposition to breast cancer, and more specifically for women in the different risk categories. Because of limited follow-up time in the MRISC study (median of 2.9 years) and relatively small numbers of cancers detected in the various risk categories, longer study follow-up is needed to give recommendations about CBE screening in these women. Also pooling with data from the Canadian study (34), using biannual CBE in *BRCA1/2* mutation carriers surveillance, and a German study (38), using biannual CBE in women with a familial or genetic predisposition to breast cancer, could give additional insight in the screening performance of CBE in these women.

BSE in women with a familial or genetic predisposition to breast cancer

Dutch guidelines recommend monthly BSE as part of the surveillance programme for women with a familial or genetic predisposition to breast cancer (39). Until now, there is no evidence from randomised controlled trials that BSE is effective in reducing breast cancer mortality in the general population (40, 41). However, evidence from clinical and epidemiological studies in the general population suggests that women who regularly and competently practise BSE are more likely to detect their breast tumours themselves and to have tumours diagnosed smaller and at a less advanced stage than women who do not practise BSE (42).

Since there are no data on the effectiveness of BSE in women with increased breast cancer

risk due to a familial or genetic predisposition, the question arises whether it is justified to teach BSE in these women. As a reflection of this controversy, there are differences in recommending monthly BSE in genetically predisposed women between different countries, partly as a result of differences in cultural norms and values (39, 43). The effectiveness of BSE in women with a familial or genetic predisposition to breast cancer may be different from the results obtained in women from the general population: women with increased breast cancer risk probably differ significantly from the general population with respect to breast cancer awareness, because of their experiences with breast (and ovarian) cancer in their family members.

Results of this thesis show that there is a subgroup of younger women performing BSE at least once a week (7% of the study population), who experience higher breast cancer-specific distress (chapter 5). As long as the Dutch guidelines still recommend BSE as part of the surveillance programme, additional counselling and care should be offered to these women. Even more important, research on the effectiveness of BSE in women with a familial or genetic predisposition to breast cancer should be done in the near future.

Comparison with alternative risk reducing strategies

Besides intensive screening, prophylactic mastectomy and prophylactic oophorectomy are alternative risk reducing strategies, especially for *BRCA1/2* mutation carriers. Prophylactic mastectomy has been shown to reduce breast cancer risk by 90% or more (44-46). Confronted by high breast cancer risk, a significant fraction of mutation carriers elects to undergo prophylactic mastectomy: in the Family Cancer Clinic of the Erasmus MC, approximately half of the unaffected *BRCA1/2* mutation carriers opts for this procedure (47). However, the use and accessibility of prophylactic surgery differs largely between countries (48). Women with *BRCA1/2* mutations who enter pre-mature menopause as the result of a risk-reducing oophorectomy also show a significant reduction in breast cancer risk, but protection is clearly incomplete (49, 50).

Despite significant risk reductions, the physical and psychological consequences of risk-reducing surgery may be unacceptable for some women. Results from studies on the impact of prophylactic mastectomy or oophorectomy on generic health-related quality of life are not available in the literature. Utility ratings of prophylactic mastectomy and oophorectomy seem low, although reduction in anxiety was not taken into account (51). Lodder et al. (52) showed that women opting for prophylactic mastectomy had significant higher distress levels than mutation carriers who opted for intensive screening, but their distress levels decreased significantly 6 months or longer after surgery, possibly due to the significant risk reduction of developing breast cancer. Most of the women who underwent prophylactic mastectomy perceived a negative impact on body image, the intimate relationship and physical well-being (52). Studies on the impact of prophylactic surgery on generic health-related quality of life in *BRCA1/2* mutation carriers may be recommended.

Another risk reducing strategy for women with increased breast cancer risk may be the use of chemoprevention, like tamoxifen and raloxifene. Although adjuvant therapy with tamoxifen appears to reduce contralateral breast cancer risk in affected *BRCA1/2* mutation carriers (53, 54), its value as primary prevention in unaffected *BRCA1/2* mutation carriers is still uncertain (55). An overview of five randomised chemoprevention trials in the general population

showed that tamoxifen cannot yet be recommended as a preventive agent, and that continued follow-up of the current trials is essential for identification of a subgroup of high-risk, healthy women for whom the risk-benefit ratio is sufficiently positive for use of tamoxifen to be recommended (56). Meanwhile, newer agents such as raloxifene and the aromatase inhibitors need to be evaluated.

Unaffected women with a *BRCA1* or *BRCA2* mutation face the choice of intensive screening, prophylactic surgery or chemoprevention. The efficacy of the various medical options and the durability of its effects are of major concern to female *BRCA1/2* mutation carriers, and will influence their choices. Although prophylactic mastectomy reduces the rate of breast cancer risk considerably, the intervention is irreversible, and may have a considerable impact on body image, sexual relations and psychological well-being. These potential harms may be unacceptable for certain women, and intensive screening is an appropriate alternative to reduce the risk of breast cancer death. Prophylactic mastectomy is less advisable with increasing age, because of the significantly declining estimated gains in life expectancy by this surgical intervention (57). For women with a clear family history of breast cancer where a mutation has not (yet) been found, intensive screening is the most appropriate risk-reducing strategy, expected to lead to significant breast cancer mortality reduction with no substantial impact on short-term generic health-related quality of life and general distress.

Estimated prevalence of women with increased breast cancer risk in the Netherlands in 2004 is 23,000 *BRCA1/2* mutation carriers, 70,000 women in the high-risk category and 70,000 women in the moderate-risk category, aged 0-60 years (chapter 9). We estimate the number of *BRCA1/2* mutation carriers undergoing prophylactic mastectomy in the Netherlands at 200-300 in the past 5 years. The total number of women with increased breast cancer risk, who is currently under intensive surveillance in the Netherlands, is estimated at 2000-2500 in year 2005. Taking into account its effectiveness and impact on short-term generic health-related quality of life and general distress, intensive screening in women with a familial or genetic predisposition to breast cancer will most probably increase further in the near future.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- Screening for breast cancer in women with a familial or genetic predisposition does not have an adverse effect on short-term generic health-related quality of life and general distress.
- Including MRI in *BRCA1/2* mutation carriers (50-85% CLTR) surveillance is cost-effective.
- For moderate-risk women (15-30% CLTR), intensive screening with only mammography, alternatively in combination with CBE, is most cost-effective.
- Longer study follow-up and pooling with data from other studies is needed to advise an optimal screening regime for high-risk women (30-50% CLTR).
- Longer study follow-up and pooling with data from other studies is needed to give recommendations about CBE screening in women with a familial or genetic predisposition to breast cancer.

Recommendations

- Estimations of the number of breast cancer deaths induced by mammography screening should be made specifically for women with a familial or genetic predisposition to breast cancer, using for example the BEIR-V risk model.
- A pilot study of alternation of mammography and MRI in screening *BRCA1/2* mutation carriers is recommended.
- Research on the effectiveness of BSE in women with a familial or genetic predisposition to breast cancer should be done.
- Longer follow-up of the MRISC study and pooling with data from other studies is recommended, in order to obtain better estimates of costs and effects of various screening regimes for the different risk groups.

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Summary

Introduction

Breast cancer is the most frequent type of cancer among women worldwide. In most Western countries the average lifetime risk for women of developing breast cancer is 8-10%. In approximately 5-10% of all breast cancer cases, a genetic predisposition is suspected. Around 25% of these cases may be attributed to the *BRCA1* and *BRCA2* breast cancer susceptibility gene mutations. Carriers of a germ-line mutation of one of these genes have a significantly increased cumulative lifetime risk (CLTR) of developing breast cancer, varying from 50 to 85%. Women from families with a clear family history of breast cancer where a mutation has not (yet) been found are also at increased risk. For *BRCA1/2* mutation carriers and women with a strong family history, the risk of breast cancer can be reduced by prophylactic mastectomy, prophylactic oophorectomy or chemoprevention. Early diagnosis as a result of intensive screening may be an alternative risk-reducing strategy.

Randomised controlled trials in the general population have shown that breast cancer screening by mammography can reduce mortality from the disease by about 25% in women aged 50-69 years. Women with increased risk for breast cancer due to a familial or genetic predisposition are often diagnosed before the age of 50 years, and effectiveness of mammography screening in this age group is uncertain. One of the reasons is that mammographic visibility of breast tumours is lower in women under 50 years because of denser breast tissue. Guidelines for screening women with increased breast cancer risk mostly consist of biannual clinical breast examination (CBE) and annual mammography, and instructions for monthly breast self-examination (BSE). These recommendations are based on expert opinion: because of ethical reasons, there has been no randomised controlled trial demonstrating its effectiveness in terms of breast cancer mortality reduction.

Prospective studies, like the Dutch MRI SCreening study (MRISC study), now have shown that intensive surveillance including magnetic resonance imaging (MRI) can detect breast cancer at an earlier stage in women with an inherited susceptibility to breast cancer. MRI

appears to be more sensitive than mammography. However, long-term effectiveness in terms of breast cancer mortality reduction of screening these women is unknown, as well as the cost-effectiveness. MRI is costly and leads to more short-term follow-up imaging and benign biopsies due to lower specificity compared to mammography. Since any method of breast-cancer screening has the potential for benefit and for harm, it is also important to pay attention to possible unfavourable side effects on health-related quality of life and distress, which may arise from the screening process.

In this thesis, the following two research questions were central:

1. What are the quality of life and psychological effects of the screening process in screening women with a familial or genetic predisposition to breast cancer?
2. What are the breast cancer mortality effects and cost-effectiveness of various screening policies, including MRI, for women with a familial or genetic predisposition to breast cancer?

Quality of life and psychological effects of the screening process in screening women with a familial or genetic predisposition to breast cancer

To investigate quality of life and psychological effects of the screening process, participants in the MRISC study were asked to complete questionnaires at different time points around screening.

Chapter 2 describes the development and testing of the Dutch Psychological Consequences Questionnaire (PCQ), by assessing the acceptability, internal consistency, scale structure and validity of the questionnaire. In the MRISC study, the PCQ was used to measure the psychological impact of breast cancer screening in women with a familial or genetic predisposition. The three subscales (emotional, physical, social) of the PCQ underwent formal linguistic and cultural translation. From our results we conclude that the PCQ is useful in measuring psychological impact among women under intensive surveillance because of increased breast cancer risk.

Chapter 3 evaluates the role of cognitive and affective risk perception in the psychological burden of breast cancer screening in women with a familial or genetic predisposition. Women with a higher affective risk perception (23% of the study population had an affective risk perception varying from high to very high) showed higher scores for general distress (Hospital Anxiety and Depression Scale, HADS, and the somatic subscale of the Symptom Checklist-90, SOM scale) and breast cancer-specific distress (Impact of Event Scale, IES), regardless of accurate cognitive risk estimation, overestimation or underestimation. Affective risk perception is a more important determinant for psychological distress than cognitive risk perception.

Chapter 4 describes the short-term effects of screening for breast cancer on generic health-related quality of life and distress, in women with a familial or genetic predisposition. A total of 519 participants in the MRISC study were asked to complete generic health-status questionnaires (SF-36, EQ-5D) as well as additional questionnaires for distress (SOM scale, role-emotional and mental health scale of the SF-36) and items relating to breast cancer screening, at three different time points around screening; 69.6% consented to participate. The study population showed significantly better generic health-related quality of life scores compared to age-/sex-adjusted reference scores from the general population. Neither generic health-related quality of life scores nor distress scores among the study sample (n=334) showed signifi-

cant changes over time. The impact of the screening process on generic health status did not differ between risk categories (*BRCA1/2* mutation carriers (50-85% CLTR), a high-risk group (30-50% CLTR) and a moderate-risk group (15-30% CLTR)). Screening these women with bi-annual CBE and annual mammography and MRI did not have a relevant impact on short-term generic health-related quality of life and general distress.

Chapter 5 examines the association between psychological distress and reported BSE frequency in women with increased breast cancer risk who are screened regularly. Two months prior to a surveillance appointment BSE frequency, general distress (HADS and SOM scale) and breast-cancer specific distress (IES) were assessed in 316 women. The majority of the women (57%) reported performing monthly BSE, 13% reported performing BSE at least once a week. Higher breast cancer-specific distress scores were observed among younger women (< 40 years) who examined their breasts at least once a week (7% of the study population), while monthly BSE is recommended.

Since MRI is a relatively new screening modality in breast cancer management, the acceptance of MRI screening is explored in chapter 6. The experience with MRI and preferences for MRI, mammography or CBE were investigated in 178 women under regular surveillance. MRI was reported to cause limited bother and to provide the most reassurance of breast cancer being absent in case of a favourable test result. MRI is acceptable as a screening test for women at increased breast cancer risk and is preferred by women over mammography.

Breast cancer mortality effects and cost-effectiveness of various screening policies, including MRI, for women with a familial or genetic predisposition to breast cancer

Long-term effectiveness in terms of breast cancer mortality reduction of screening women with increased breast cancer risk is still unknown from ongoing studies. Therefore the MISCAN breast cancer-screening model, which has been successfully applied in the evaluation of different cancer-screening programmes, was used to predict effectiveness and cost-effectiveness of various screening policies for these women, with MRI, mammography and CBE as possible screening modalities. Since no randomised controlled trial of CBE compared to no screening has been completed, the Canadian National Breast Screening Study-2 (CNBSS-2) was used to estimate stage-specific CBE sensitivities.

In chapter 7 a model evaluation of the CNBSS-2 is conducted. The CNBSS-2 was a randomised controlled trial in women aged 50-59 years, designed to evaluate the efficacy of annual mammography over and above annual CBE. Because the control arm was screened (annual CBE), no estimations of mammography benefit compared to no screening could be made, as is available from other mammography trials, nor any estimate of the benefit of CBE screening. We incorporated demographic, epidemiological, and screening characteristics of the CNBSS-2 in MISCAN. Stage-specific sensitivities of CBE alone, CBE supplemented with mammography, and breast cancer incidence rate in the trial were estimated by comparing observed trial data with model predictions. We estimated a 24% to 29% higher breast cancer incidence rate in the CNBSS-2 than the average Canadian rate. Estimated sensitivity of CBE (control arm) varied from 0.29 to 0.48 for stage T1c and from 0.60 to 0.65 for stage T2+. Estimated sensitivity of CBE supplemented with mammography (study arm) varied from 0.50 to 0.79 for stage T1c and was 0.95 for stage T2+. Expected breast cancer mortality reduction by annual CBE screening was 20.5% compared to no screening. The estimated breast cancer

mortality reduction by mammography screening compared to no screening for the CNBSS-2 fell within the range of 13.6% to 34.1%.

Since the usefulness of CBE as a screening modality is uncertain, chapter 8 explores the effectiveness and cost-effectiveness of CBE screening when implemented in the Dutch nation-wide screening programme, as well as the usefulness of adding CBE to mammography screening. Estimated stage-specific sensitivities of CBE, resulting from the model evaluation of the CNBSS-2 (chapter 7), were used. Biennial CBE screening programmes can be more cost-effective than high-quality biennial mammography screening programmes, but our estimate of reduced effectiveness of CBE advises against its use for screening, either alone or in addition to mammography, in developed countries. For developing countries with relatively low costs for CBE, CBE screening may be an appropriate policy.

Chapter 9 predicts the effectiveness and cost-effectiveness of alternative screening policies for three risk categories: *BRCA1/2* mutation carriers (50-85% CLTR), a high-risk (30-50% CLTR) and a moderate-risk group (15-30% CLTR). The MISCAN breast cancer-screening model was used to simulate the MRISC study, and to predict costs and effects of screening strategies. We constructed three risk-specific models corresponding to the three risk categories. With screening data from the MRISC study we estimated stage-specific sensitivity of different screening tests and resulting stage-shift by screen detection, which were incorporated into these models. Benefit of early detection was based on modelling estimates and pooled analyses of randomised mammography screening trials. Intensive surveillance including MRI in *BRCA1/2* mutation carriers is estimated to reduce breast cancer mortality by 50.1%, compared to 40.7% by mammography and clinical breast examination (CBE) only. Its effectiveness is almost twice as high compared to biennial mammography screening in women from age 50 with average risk (8-10%). Screening *BRCA1/2* mutation carriers with biannual CBE and annual mammography and MRI from age 30 to 60 is at a cost of € 4,314 per life-year gained (3% discounting). Offering MRI and mammography alternately at a 6 months interval is even more cost-effective. For the moderate-risk group, screening regimes with only mammography, alternatively in combination with CBE, from age 40 to 50 years are most favourable in terms of cost-effectiveness (range € 3,080 - € 4,764), and may lead to 24.5-30.7% breast cancer mortality reduction. Observed breast cancer incidence in the high-risk group did not differ substantially from the moderate-risk group. For the high-risk group we were unable to draw firm conclusions for or against including MRI in screening.

Discussion

In Chapter 10 additional aspects of screening women with a familial or genetic predisposition to breast cancer are discussed.

Women with increased risk for breast cancer due to a familial or genetic predisposition are often diagnosed before the age of 50. Results from chapter 9 lead to a recommendation to start screening these women at age 30 or 40 years, depending on the CLTR of developing breast cancer. Since breast tissue is more sensitive to radiation in younger women and younger women have a longer life expectancy, an important determinant of radiation risk in breast cancer screening is age of screening. In the near future, estimations of the number of breast cancer deaths induced by mammography screening should be made specifically for women with a familial or genetic predisposition to breast cancer, using for example the BEIR-

V model, and presented mortality effects and cost-effectiveness of various screening policies may be adjusted.

The effectiveness and cost-effectiveness of alternative screening policies for the high-risk category (30-50% CLTR) were not calculated: breast cancer incidence in the high-risk group of the MRISC study was much lower than predicted (chapter 9), and was even lower than the incidence in the moderate-risk category (15-30% CLTR). More research on the risk assessment and risk categorisation of women in the high-risk group is warranted to explain the observed results. Besides, longer follow-up of the MRISC study or pooling with data from other studies is needed to advise a screening regime for this risk category.

When mammography and MRI screening is alternated, MRI might be used as additional follow-up when results of mammography screening are uncertain or suspicious. A pilot study of alternation of mammography and MRI in screening *BRCA1/2* mutation carriers could give insight in the use of follow-up by MRI, ultrasonography, fine-needle aspiration and biopsy. Cost-effectiveness of offering mammography and MRI alternately at a 6 months interval could be re-estimated, using this information.

Opposite results about the screening performance of CBE give rise to the question whether it is justified to use CBE as a screening modality for women with a familial or genetic predisposition to breast cancer, and more specifically for women in the different risk categories. Because of limited follow-up time in the MRISC study (median of 2.9 years) and relatively small numbers of cancers detected in the various risk categories, longer study follow-up and pooling with data from other studies is needed to give recommendations about CBE screening in these women.

Dutch guidelines recommend monthly BSE as part of the surveillance programme for women with a familial or genetic predisposition to breast cancer. Since there are no data on the effectiveness of BSE in these women, research on this topic should be done in the near future.

Unaffected women with a *BRCA1* or *BRCA2* mutation now face the choice of intensive screening, prophylactic surgery or chemoprevention. The efficacy of the various medical options and the durability of its effects are of major concern to female *BRCA1/2* mutation carriers, and will influence their choices. Although prophylactic mastectomy reduces the rate of breast cancer risk by 90% or more, the intervention is irreversible, and may have a considerable impact on body image, sexual relations and psychological well-being. These potential harms may be unacceptable for certain women, and intensive screening is an appropriate alternative to reduce the risk of breast cancer death. Prophylactic mastectomy is less advisable with increasing age, because of the significantly declining estimated gains in life expectancy by this surgical intervention. For women with a clear family history of breast cancer where a mutation has not (yet) been found, intensive screening is the most appropriate risk-reducing strategy, expected to lead to significant breast cancer mortality reduction with no substantial impact on short-term generic health-related quality of life and general distress.

Conclusions

- Screening for breast cancer in women with a familial or genetic predisposition does not have an adverse effect on short-term generic health-related quality of life and general distress.

- Including MRI in *BRCA1/2* mutation carriers (50-85% CLTR) surveillance is cost-effective.
- For moderate-risk women (15-30% CLTR), intensive screening with only mammography, alternatively in combination with CBE, is most cost-effective.
- Longer study follow-up and pooling with data from other studies is needed to advise an optimal screening regime for high-risk women (30-50% CLTR).
- Longer study follow-up and pooling with data from other studies is needed to give recommendations about CBE screening in women with a familial or genetic predisposition to breast cancer.

Samenvatting

Inleiding
Borstkanker is wereldwijd de meest voorkomende vorm van kanker bij vrouwen. In de meeste westerse landen hebben vrouwen een lifetime-risico van gemiddeld 8-10% om borstkanker te krijgen. Bij ongeveer 5-10% van alle gevallen van borstkanker is mogelijk sprake van een genetische predispositie. Circa 25% van deze gevallen kan worden toegeschreven aan een mutatie van het *BRCA1* of *BRCA2* gen. Draagsters van een kiembaanmutatie van één van deze genen hebben een aanzienlijk hoger cumulatief lifetime-risico (CLTR) om borstkanker te krijgen, variërend van 50 tot 85%. Ook vrouwen met een belaste familie waarbij (nog) geen mutatie gevonden is, hebben een verhoogd risico om borstkanker te krijgen. Draagsters van een *BRCA1/2* mutatie en vrouwen met een belaste familieanamnese kunnen het risico op borstkanker verlagen door profylactische mastectomie, profylactische ovariëctomie of chemopreventie. Vroegdiagnostiek door intensieve screening is mogelijk een alternatieve risicoverlagende strategie.

Uit gerandomiseerde studies in de algemene bevolking blijkt dat screening met mammografie de sterfte aan borstkanker bij vrouwen van 50-69 jaar met ongeveer 25% kan verminderen. Bij vrouwen met een verhoogd risico op borstkanker als gevolg van een belaste familieanamnese of gendragerschap wordt de diagnose vaak gesteld vóór de leeftijd van 50 jaar. In deze leeftijdsgroep is de effectiviteit van screening met mammografie onzeker, onder andere omdat bij vrouwen onder de 50 tumoren in de borst minder goed zichtbaar zijn op het mammogram vanwege dichter borstklierweefsel. Richtlijnen voor het screenen van vrouwen met een verhoogde kans op borstkanker bestaan meestal uit halfjaarlijks palpatieonderzoek door de arts (*clinical breast examination,* CBE), jaarlijkse mammografie, en instructies voor maandelijks borstzelfonderzoek (*breast self-examination,* BSE). Deze aanbevelingen zijn gebaseerd op de mening van deskundigen; de effectiviteit van deze richtlijnen in termen van een daling van borstkankersterfte is om ethische redenen nooit in een gerandomiseerde studie onderzocht.

Prospectieve onderzoeken, waaronder de Nederlandse MRI SCreening studie (MRISC stu-

die), hebben laten zien dat door intensieve surveillance met *magnetische resonantie 'imaging'* (MRI), borstkanker in een vroeger stadium kan worden ontdekt bij vrouwen met een erfelijke of familiaire belasting. De sensitiviteit van MRI blijkt hoger dan die van mammografie. Het is onbekend of het screenen van deze vrouwen op lange termijn effectief is en tot een daling van de sterfte aan borstkanker leidt; ook de kosteneffectiviteit is niet bekend. MRI is duur en leidt op korte termijn tot een toename van beeldvormende follow-up en benigne biopsieën omdat MRI een lagere specificiteit heeft dan mammografie. Omdat iedere methode van borstkankerscreening zowel voor- als nadelen heeft, is het ook belangrijk om aandacht te besteden aan de eventuele nadelige neveneffecten van het screeningsproces op gezondheidsgerelateerde kwaliteit van leven (*health-related quality of life,* HRQoL) en stress.

In dit proefschrift staan de twee volgende onderzoeksvragen centraal:

1. Wat zijn de effecten op kwaliteit van leven en de psychologische effecten van het screeningsproces bij vrouwen met een familiaire of genetische predispositie voor borstkanker?
2. Wat is het effect op borstkankersterfte en wat is de kosteneffectiviteit van verschillende screeningsstrategieën, waaronder MRI, bij vrouwen met een familiaire of genetische predispositie voor borstkanker?

Effecten op kwaliteit van leven en psychologische effecten van het screeningsproces bij vrouwen met een familiaire of genetische predispositie voor borstkanker

Om effecten op kwaliteit van leven en psychologische effecten van het screeningsproces te onderzoeken, is aan deelneemsters aan de MRISC studie gevraagd om een vragenlijst in te vullen op verschillende momenten rondom de screening.

Hoofdstuk 2 beschrijft de ontwikkeling van de Nederlandse versie van de *Psychological Consequences Questionnaire* (PCQ) en de toetsing hiervan door onderzoek naar de aanvaardbaarheid, interne consistentie, schaalstructuur en validiteit van de vragenlijst. De PCQ is in de MRISC studie gebruikt om de psychologische impact van borstkankerscreening bij vrouwen met een familiaire of genetische predispositie te meten. De drie subschalen van de PCQ (emotioneel, lichamelijk, sociaal) zijn volgens officiële procedures taalkundig en cultureel vertaald. Op grond van onze resultaten concluderen we dat de PCQ geschikt is om de psychologische impact te meten bij vrouwen die onder intensieve controle staan vanwege een verhoogde kans op borstkanker.

In hoofdstuk 3 wordt onderzocht welke rol de cognitieve en affectieve risicoperceptie spelen bij de psychische belasting door screening, bij vrouwen met een familiaire of genetische predispositie voor borstkanker. Vrouwen met een hogere affectieve risicoperceptie (23% van de onderzoekspopulatie had een hoge tot zeer hoge affectieve risicoperceptie) hadden hogere scores voor algemene stress (*Hospital Anxiety and Depression Scale,* HADS, en de somatische subschaal van de *Symptom Checklist-90,* SOM schaal) en borstkankerspecifieke stress (*Impact of Event Scale,* IES), ongeacht een adequate, te hoge of te lage cognitieve risicoschatting. De affectieve risicoperceptie is een belangrijkere determinant voor psychische stress dan de cognitieve risicoperceptie.

Hoofdstuk 4 beschrijft de kortetermijneffecten van borstkankerscreening op generieke HR-QoL en stress, bij vrouwen met een familiaire of genetische predispositie. In totaal werd aan 519 deelneemsters aan de MRISC studie gevraagd om op drie verschillende momenten rond-

om de screening vragenlijsten in te vullen: generieke vragenlijsten over hun gezondheidstoestand (SF-36, EQ-5D), enkele aanvullende vragen over stress (SOM schaal en de schalen Emotioneel Functioneren en Mentale Gezondheid van de SF-36) en items over het screenen op borstkanker; 69,6% stemde toe in deelname. De scores voor generieke HRQoL waren in de onderzoekspopulatie significant hoger dan de voor leeftijd en geslacht gecorrigeerde referentiescores in de algemene bevolking. Noch de scores voor generieke HRQoL noch de scores voor stress in de onderzoekspopulatie (n=334) lieten statistisch significante veranderingen over de tijd zien. De invloed van het screeningsproces op generieke HRQoL verschilde niet tussen risicogroepen (*BRCA1/2* mutatie draagsters (50-85% CLTR), een hoog-risico groep (30-50% CLTR) en een matig-risico groep (15-30% CLTR)). Screening met halfjaarlijkse CBE en jaarlijkse mammografie en MRI had op korte termijn geen belangrijke invloed op generieke HRQoL en algemene stress.

Hoofdstuk 5 gaat in op het verband tussen psychische stress en de gerapporteerde frequentie van BSE bij vrouwen met een verhoogd risico op borstkanker die regelmatig worden gescreend. Twee maanden vóór een controleafspraak werden de frequentie van BSE, algemene stress (HADS en SOM schaal) en borstkankerspecifieke stress (IES) bij 316 vrouwen onderzocht. De meerderheid van de vrouwen (57%) gaf aan maandelijks BSE te doen, 13% deed minstens één keer per week BSE. Jongere vrouwen (< 40 jaar) die hun borsten minstens één keer per week onderzochten (terwijl de aanbeveling is om dit maandelijks te doen), hadden hogere scores voor borstkankerspecifieke stress.

Omdat MRI een relatief nieuwe methode is voor vroege opsporing van borstkanker, wordt in hoofdstuk 6 aandacht besteed aan de aanvaardbaarheid van MRI screening. Aan 178 vrouwen onder periodieke controle is gevraagd naar hun ervaringen met MRI en hun voorkeur voor MRI, mammografie of CBE. MRI bleek weinig ongemak te veroorzaken en gaf de vrouw in geval van een gunstig testresultaat de meeste zekerheid over de afwezigheid van borstkanker. MRI is aanvaardbaar als screeningstest voor vrouwen met een verhoogde kans op borstkanker en heeft bij vrouwen de voorkeur boven mammografie.

Effect op borstkankersterfte en kosteneffectiviteit van verschillende screeningsstrategieën, waaronder MRI, bij vrouwen met een familiaire of genetische predispositie voor borstkanker

De resultaten van lopend onderzoek naar de langetermijneffectiviteit (in termen van een daling van borstkankersterfte) van het screenen van vrouwen met een verhoogd risico op borstkanker, zijn nog onbekend. Daarom gebruikten wij het MISCAN model voor borstkankerscreening, dat met succes is toegepast bij de evaluatie van verschillende programma's voor borstkankerscreening, om voor deze vrouwen de effectiviteit en de kosteneffectiviteit te voorspellen van verschillende screeningstrategieën met MRI, mammografie en CBE als mogelijke screeningsmethoden. Omdat gerandomiseerde studies naar CBE in vergelijking met een situatie zonder screening niet zijn afgerond, werd de *Canadian National Breast Screening Study-2* (CNBSS-2) gebruikt voor een schatting van de stadiumspecifieke sensitiviteit van CBE.

In hoofdstuk 7 wordt een modelevaluatie van de CNBSS-2 uitgevoerd. De CNBSS-2 is een gerandomiseerde studie naar de effectiviteit van jaarlijkse mammografie als aanvulling op jaarlijkse CBE bij vrouwen van 50-59 jaar. Omdat de controle arm werd gescreend met jaarlijkse CBE, kan het voordeel van screening door middel van mammografie ten opzichte van

een situatie zonder screening niet worden geschat, zoals in andere mammografie-studies wel mogelijk is; dit geldt ook voor het voordeel van screening door middel van CBE. We namen de demografische, epidemiologische en screeningskenmerken van de CNBSS-2 op in het MISCAN model. De stadiumspecifieke sensitiviteit van alleen CBE, van CBE in combinatie met mammografie, en de incidentie van borstkanker in de studie werden geschat door de geobserveerde data in de studie te vergelijken met de modelvoorspellingen. We schatten de incidentie van borstkanker in de CNBSS-2 24 tot 29% hoger dan de gemiddelde incidentie in Canada. De geschatte sensitiviteit van CBE (controle arm) varieerde van 0,29 tot 0,48 voor stadium T1c en van 0,60 tot 0,65 voor stadium T2+. De geschatte sensitiviteit van CBE in combinatie met mammografie (studie arm) varieerde van 0,50 tot 0,79 voor stadium T1c en was 0,95 voor stadium T2+. De verwachte reductie in borstkankersterfte door jaarlijkse screening met CBE was 20.5% ten opzichte van een situatie zonder screening. De verwachte daling van sterfte aan borstkanker door screening met mammografie in de CNBSS-2 lag tussen de 13,6 en 34,1%.

Omdat onduidelijk is of CBE als screeningsinstrument nuttig is, worden in hoofdstuk 8 de effectiviteit en de kosteneffectiviteit van CBE, wanneer gebruikt in het Nederlandse bevolkingsonderzoek naar borstkanker, onderzocht. Daarnaast is gekeken naar het nut van toevoeging van CBE aan screening met mammografie. Hiervoor werden de met het MISCAN model geschatte stadiumspecifieke sensitiviteiten van CBE in de CNBSS-2 (hoofdstuk 7) gebruikt. Een screeningsprogramma met tweejaarlijkse CBE kan kosteneffectiever zijn dan een kwalitatief hoogstaand programma met tweejaarlijkse mammografie. Echter, de door ons geschatte lagere effectiviteit van CBE pleit tegen het gebruik van CBE, alleen of in combinatie met mammografie, voor de screening op borstkanker in ontwikkelde landen. In ontwikkelingslanden waar de kosten voor CBE relatief laag zijn, is screening met CBE mogelijk wel geschikt.

In hoofdstuk 9 worden de effectiviteit en de kosteneffectiviteit voorspeld van alternatieve screeningsstrategieën voor drie risicogroepen: *BRCA1/2* mutatie draagsters (50-85% CLTR), een hoog-risico groep (30-50% CLTR) en een matig-risico groep (15-30% CLTR). Het MISCAN model voor borstkankerscreening werd gebruikt om de MRISC studie te simuleren, en de kosten en effecten van de verschillende screeningsstrategieën te voorspellen. We maakten drie risicospecifieke modellen die overeenkwamen met de drie risicocategorieën. Op basis van de screeningsgegevens uit de MRISC studie werd een schatting gemaakt van de stadiumspecifieke sensitiviteit van de verschillende screeningstesten en de verschuiving in de stadiumverdeling als gevolg van screening; deze namen we op in het model. Het voordeel van vroegtijdige ontdekking was gebaseerd op modelschattingen en gepoolde analyses van gerandomiseerde mammografie-studies. Intensieve surveillance met MRI bij *BRCA1/2* mutatie draagsters zal de sterfte aan borstkanker met naar schatting 50,1% verlagen, ten opzichte van 40.7% door surveillance met alleen mammografie en CBE. De effectiviteit hiervan is bijna twee keer zo groot als de effectiviteit van de tweejaarlijkse screening met mammografie bij vrouwen van 50 jaar of ouder met een gemiddeld risico (8-10%). Screening van *BRCA1/2* mutatie draagsters in de leeftijd van 30 tot 60 jaar met halfjaarlijkse CBE en jaarlijkse mammografie en MRI kost € 4.314 per gewonnen levensjaar (3% discontering). Het afwisselend aanbieden van MRI en mammografie met een interval van 6 maanden is zelfs nog kosteneffectiever. Voor de matig-risico groep heeft een screeningsprogramma met mammografie, alleen of in combinatie met CBE, voor vrouwen van 40 tot 50 jaar de gunstigste kosteneffectiviteit (range € 3.080 -

€ 4.764), en kan leiden tot een reductie in borstkankersterfte van 24,5 tot 30,7%. De geobserveerde borstkankerincidentie in de hoog-risico groep verschilde nauwelijks van de incidentie in de matig-risico groep. Het was niet mogelijk om harde conclusies te trekken voor of tegen screening met MRI in de hoog-risico groep.

Discussie

Hoofdstuk 10 gaat in op een aantal andere aspecten van het screenen van vrouwen met een familiaire of genetische predispositie voor borstkanker.

Vaak wordt bij vrouwen met een verhoogde kans op borstkanker als gevolg van een familiaire of genetische predispositie al voor de leeftijd van 50 jaar borstkanker vastgesteld. De resultaten van hoofdstuk 9 leiden tot de aanbeveling om met het screenen van deze vrouwen te beginnen zodra zij 30 of 40 jaar zijn, afhankelijk van hun CLTR om borstkanker te ontwikkelen. Omdat het borstklierweefsel bij jongere vrouwen gevoeliger is voor straling en jongere vrouwen een grotere levensverwachting hebben, is de screeningsleeftijd een belangrijke determinant van het stralingsrisico. Speciaal voor vrouwen met een familiaire of genetische predispositie voor borstkanker moet in de nabije toekomst een schatting worden gemaakt van het aantal sterfgevallen ten gevolge van door mammografische screening geïnduceerde borstkanker, bijvoorbeeld door gebruik te maken van het BEIR-V model, en moeten de beschreven effecten van de verschillende screeningsstrategieën op de sterfte en de kosteneffectiviteit worden aangepast.

De effectiviteit en kosteneffectiviteit van alternatieve screeningsstrategieën zijn niet berekend voor de hoog-risico groep (30-50% CLTR), omdat in de MRISC studie de incidentie van borstkanker in deze groep veel lager was dan voorspeld (hoofdstuk 9) en zelfs lager dan de incidentie in de matig-risico groep (15-30% CLTR). Nader onderzoek naar de risico-inschatting en de risico-indeling van vrouwen in de hoog-risico groep is nodig om de waargenomen resultaten te verklaren. Bovendien zijn een langere follow-up duur van de MRISC studie of pooling met gegevens van andere onderzoeken nodig om een advies te kunnen geven over de optimale screeningsstrategie in deze risicogroep.

Als afwisselend met mammografie of MRI wordt gescreend, zou MRI kunnen worden gebruikt als aanvullende follow-up wanneer het mammografisch screeningsonderzoek een uitslag “onzeker” of “verdacht” geeft. Een pilot onderzoek waarbij *BRCA1/2* mutatie draagsters afwisselend met mammografie of MRI worden gescreend, zal inzicht geven in het gebruik van MRI, echografie, FNA (dunnenaaldbiopsie) en biopsie als mogelijke follow-up. Op grond van deze informatie kan een nieuwe schatting worden gemaakt van de kosteneffectiviteit van screening met afwisselend mammografie of MRI met een interval van 6 maanden.

Tegenstrijdige resultaten met betrekking tot de prestaties van screening met CBE leiden tot de vraag of het gerechtvaardigd is om CBE te gebruiken als screeningsmodaliteit voor vrouwen met een familiaire of genetische predispositie voor borstkanker in het algemeen, en voor de verschillende risicogroepen in het bijzonder. Gezien de beperkte follow-upduur van de MRISC studie (mediaan 2,9 jaar) en de relatief kleine aantallen ontdekte kankers in de verschillende risicogroepen, zijn een langere follow-up duur en pooling met gegevens van andere onderzoeken noodzakelijk om te kunnen adviseren over het screenen van deze vrouwen met CBE.

De Nederlandse richtlijnen bevelen maandelijks BSE aan als onderdeel van de periodieke

surveillance voor vrouwen met een familiaire of genetische predispositie voor borstkanker. Omdat onbekend is of BSE bij deze vrouwen effectief is, moet dit in de nabije toekomst worden onderzocht.

Vrouwen met een *BRCA1* of *BRCA2* mutatie die (nog) geen borstkanker hebben, kunnen tegenwoordig kiezen tussen intensieve screening, profylactische chirurgie of chemopreventie. De effectiviteit van de verschillende klinische mogelijkheden en de duurzaamheid van het effect zijn voor *BRCA1/2* mutatie draagsters van groot belang en zullen hun keuze beïnvloeden. Alhoewel met profylactische mastectomie de kans op borstkanker met 90% of meer afneemt, is deze ingreep onomkeerbaar en kan grote invloed hebben op het lichaamsbeeld, de seksuele relaties en het psychisch welbevinden. Deze nadelen zijn voor sommige vrouwen onaanvaardbaar; intensieve screening is dan een geschikt alternatief om hun kans om aan borstkanker te overlijden, te verlagen. Preventieve mastectomie is op latere leeftijd minder geschikt vanwege de aanzienlijk lagere geschatte winst in levensverwachting door deze interventie. Voor vrouwen met een belaste familie waarbij (nog) geen mutatie gevonden is, is intensieve screening het meest geschikte alternatief: het leidt naar verwachting tot een aanzienlijke daling van de borstkankersterfte met op korte termijn geen substantieel effect op generieke HRQoL en algemene stress.

Conclusies

- Screening op borstkanker bij vrouwen met een familiaire of genetische predispositie heeft geen negatieve kortetermijneffecten op generieke HRQoL en algemene stress.
- Het is kosteneffectief om MRI te gebruiken bij de surveillance van *BRCA1/2* mutatie draagsters (50-85% CLTR).
- Voor vrouwen met een matig risico (15-30% CLTR) is intensieve screening met alleen mammografie, eventueel in combinatie met CBE, het meest kosteneffectief.
- Een langere follow-up duur en pooling met gegevens van andere studies zijn nodig om een aanbeveling te kunnen doen voor een optimaal screeningsbeleid voor vrouwen met een hoog risico (30-50% CLTR).
- Een langere follow-up duur en pooling met gegevens van andere studies zijn nodig om een advies te kunnen geven over screening met CBE bij vrouwen met een familiaire of genetische predispositie voor borstkanker.

Publications

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En dan nu ……. op naar de volgende bevalling!

Curriculum vitae

Rian Rijnsburger werd geboren op 5 september 1969 in Lekkerkerk, als oudste van vier kinderen en als dochter van een bakker. In 1987 behaalde zij het VWO-diploma aan de Christelijke Scholengemeenschap Comenius in Capelle aan den IJssel. In datzelfde jaar begon zij met haar studie Economie aan de Erasmus Universiteit Rotterdam. Gedurende haar studie kreeg zij specifieke interesse voor de gezondheidszorg, en in 1997 behaalde zij het vrij doctoraal examen Economie, waarbij zij verschillende keuzevakken van de studie Beleid en Management Gezondheidszorg in het curriculum inbracht. Tijdens haar studie werkte zij een jaar als onderzoeksassistent bij het Instituut voor Medische Technology Assessment, Erasmus Universiteit Rotterdam (later: Erasmus MC, Universitair Medisch Centrum Rotterdam). Vanaf 1997 werkte zij als wetenschappelijk onderzoeker voor ditzelfde instituut. Na een jaar als datamanager te hebben gewerkt (Onze Lieve Vrouwe Gasthuis, Amsterdam), begon zij in januari 2000 bij de afdeling Maatschappelijke Gezondheidszorg, Erasmus MC, Universitair Medisch Centrum Rotterdam. Hier werkte zij aan het project 'Impact van regelmatige controle (screening) bij vrouwen met een verhoogd risico op borstkanker vanwege een familiaire predispositie', wat resulteerde in dit proefschrift. Van 1999 tot 2001 volgde zij de postdoctorale opleiding Epidemiologie aan het EMGO-instituut van het VU Medisch Centrum, Amsterdam, waarvan zij in 2001 het diploma behaalde. Vanaf juni 2005 werkt zij als wetenschappelijk onderzoeker bij de Werkgroep Erfelijke Tumoren, Afdeling Interne Oncologie van de Daniel den Hoed Kliniek, Erasmus MC, Universitair Medisch Centrum Rotterdam. Zij zet daar het onderzoek naar de lange-termijn effectiviteit van borstkankerscreening bij jonge vrouwen met een verhoogd risico vanwege een genetische / familiaire predispositie voort.

Rian Rijnsburger is getrouwd met Martijn Blom, en zij hebben samen een zoon, Niels (1 jaar).