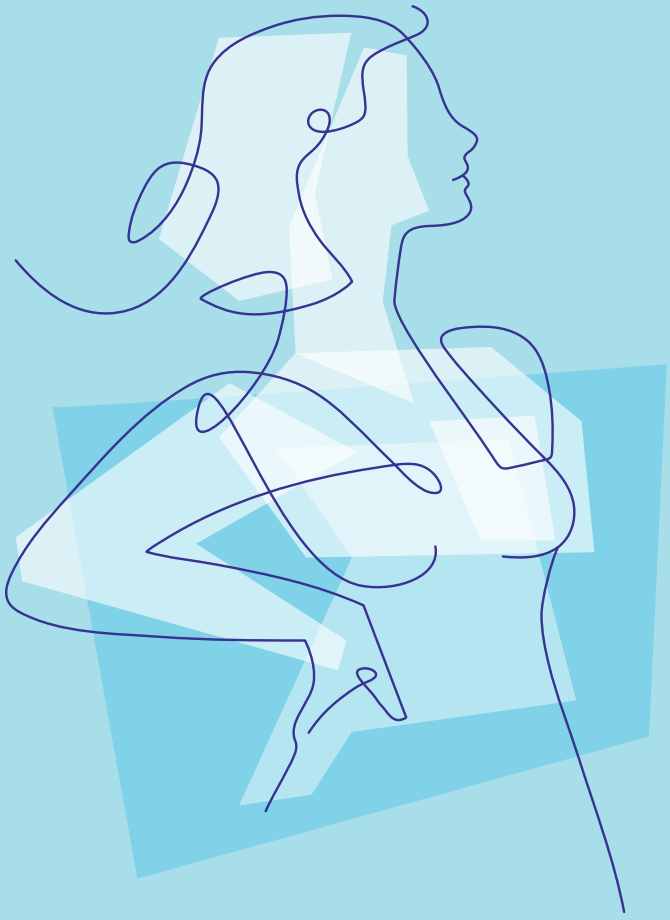

Effectiveness and Perspectives of Women in the Dutch Breast Cancer Screening Programme

LINDY M. KREGTING

Effectiveness and Perspectives of Women in the Dutch Breast Cancer Screening Programme

Lindy Kregting

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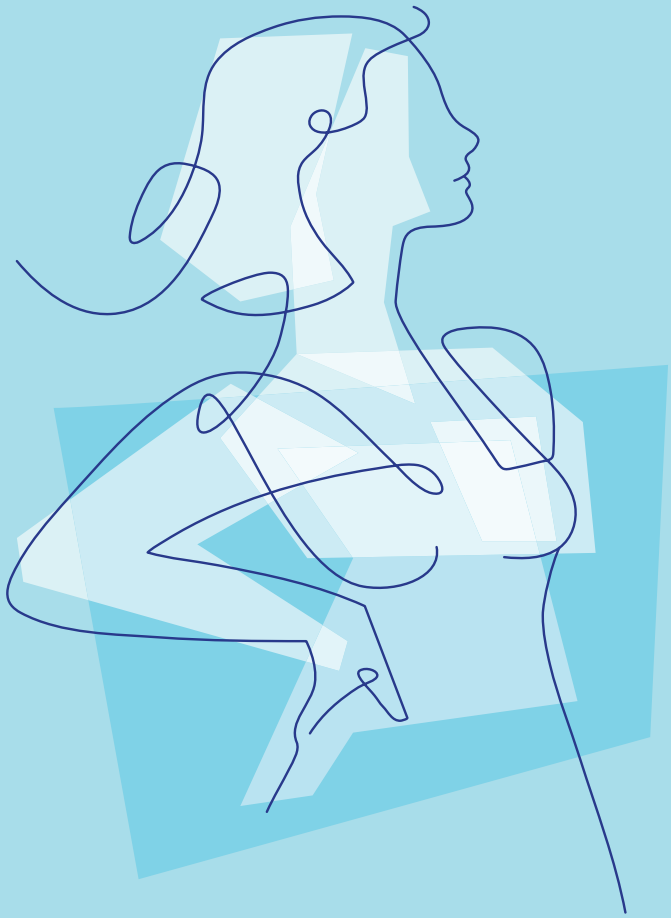


1

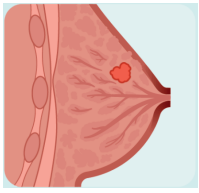
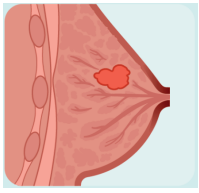
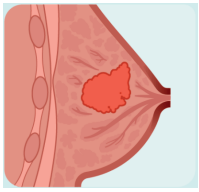
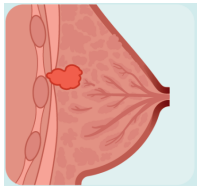
Introduction

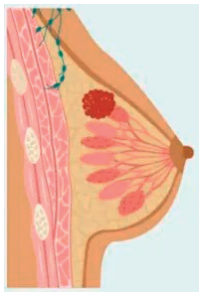
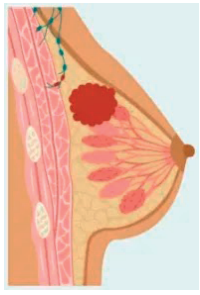
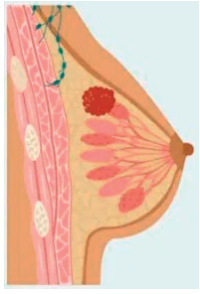
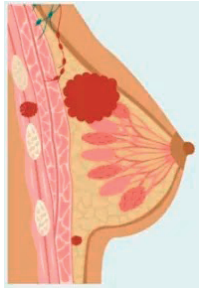
BREAST CANCER

Pathology

Breast cancer is the uncontrollable growth of body cells into a malignant tumour located in the breast tissue caused by damaged DNA. The uncontrollable growth can start in either the milk ducts, lobules (milk producing glands), or the connective tissue between these ducts and lobules. Most often, breast cancer starts in the milk ducts and as long as it remains in there, it is called ductal carcinoma in situ (DCIS). A breast cancer becomes invasive whenever the tumour grows into surrounding tissue. Eventually, breast cancer can spread to other parts of the body (metastasize) through blood vessels and/or lymph vessels.

In clinical settings, breast cancer stages are classified using the tumour, node, metastasis (TNM) classification system: the size of the tumour (T), possible regional lymph node involvement (N), and possible distant metastasis (M) are defined (Table 1).

Tumour size (T)	
T1: 2cm or less in diameter	
T2: 2-5 cm	
T3: 5cm or more	
T4: tumour of any size growing into the chest wall	

Regional lymph node involvement (N)	
N0: lymph nodes uninvolved	
N1+: number of lymph nodes involved	
Distant metastasis (M)	
M0: no distant metastasis	
M1: distant metastasis	

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Risk factors

Some risk factors have been identified to influence the risk of developing breast cancer. The factor with the largest influence is sex with less than 1% of all breast cancers being detected in men.[3] Furthermore, age is an important risk factor, because a longer life gives more opportunities for DNA damage and less effectiveness in DNA repair. Most breast cancers are detected in women between the age of 50 and 75.[3] In addition, familial heritage in the form of genetic mutations (e.g. BRCA1 and BRCA2, but also CHECK2, ATM and PALB2) increases the risk of developing breast cancer considerably.[4] Next to that, a high density of the breast tissue (i.e. relative amount of glandular tissue compared to fat tissue) increases breast cancer risk.[5, 6]

Other factors that are known to increase breast cancer risk are reproductive factors like advanced age at first birth, nulliparity, and low age at menarche, and lifestyle factors like high BMI, lack of physical activity, and excessive alcohol consumption.[7-11] On the other hand, parity, breastfeeding, and young age at menopause have been found to be associated with a lower than average risk of developing breast cancer.[7, 12] However, these reproductive and lifestyle factors only slightly increase or decrease the risk of developing breast cancer, which means that many women who develop breast cancer do not have any evident risk factors other than being a woman and being of older age. Women who have many children and/or breastfeed for a total period longer than 12 months in their lifetime, do have a substantially reduced risk of developing breast cancer.[12]

Incidence

In 2018, an estimate of 2.1 million new breast cancer cases were diagnosed worldwide.[13] Therefore, breast cancer accounted for almost one in four cancer cases among women. In the Netherlands, 17,188 women were diagnosed with breast cancer in 2020 which represents 30.4% of all cancer diagnoses in women that year.[3] Over the last decades the incidence of breast cancer steadily increased (figure 1A).[14] The increase starting in 1989 can be explained by the start of the national breast cancer screening programme, which typically leads to an increase in newly diagnosed cases (incidence). After implementation was complete, incidence showed a decrease, until 1998 when the upper age of the screening programme was extended to age 74 years. Following this, the incidence continued to increase, likely due to an increase in prevalence of risk factors in the population such as more obesity and higher age at first birth. In 2020, a significant drop in diagnoses was seen due to a screening disruption of a few months and less clinical detections because of the COVID-19 pandemic.[15]

Treatment

The treatment of patients with breast cancer depends on the stage at diagnosis and some tumour specifics, like hormone sensitivity. However, almost all patients get treatment and most of them start with surgery.[16] Most often breast-conserving surgery (lumpectomy) is sufficient to remove the tumour, but sometimes a mastectomy is needed.[16] Generally, surgery is followed by radiotherapy. Additionally, the majority of women receive adjuvant systemic treatment which can consist of hormonal therapy, chemotherapy, targeted therapy, immunotherapy or a combination of these. The effectiveness of adjuvant therapy increased significantly over the last decades.[17] This improved the survival of breast cancer patients, and also reduced the risk of recurrence and metastasis.[17] More recently, neo-adjuvant treatment has been added as a treatment option in which adjuvant treatment is already given before surgery. This reduces the size of the tumour before surgery, which allows for less extensive surgery and a reduction in postoperative complications.[18]

Mortality

In 2019, 3,056 women and 21 men died of breast cancer in the Netherlands.[3] Even though the incidence of breast cancer increased over the years, the absolute mortality slowly decreased.[3] When looking at the age-standardised rate based on the European standard population (ESR), the decrease in mortality is steeper; moving from 38.98 per 100,000 in 1989 to 33.54 in 2000 and 21.26 in 2020 (figure 1B).[3, 14] This decrease in mortality can be attributed both to advances in (adjuvant) treatment and implementation and improvements in the screening programme.[19, 20] However, chances of survival are still largely dependent on the stage at diagnosis.[21, 22] This resulted in a 10-year overall survival rate of 93% for early breast cancer, 62% for locally advanced cancers, and 9% for metastatic breast cancer in Dutch women.[22]

Figure 1 A) Absolute breast cancer incidence in the Netherlands from 1989 to 2022 and B) breast cancer mortality European standardised rate (ESR) in the Netherlands from 1989 to 2021* (14)*
** data from 2021 and 2022 are interim data*

BREAST CANCER SCREENING

Breast cancer screening programmes invite asymptomatic women with an average risk of developing breast cancer for a screening test multiple times over a certain age range. Most countries who implemented breast cancer screening programmes now use digital mammography to investigate the breasts of these women, however also film-based mammography and clinical breast examination are still used.[23] The European Commission Initiative on Breast Cancer (ECIBC) strongly recommends biennial mammography screening for women between the ages of 50 and 69.[24] On top of that, they suggest biennial or triennial mammography screening for the ages 45 to 49 and triennial mammography screening for the ages 70 to 74.[24]

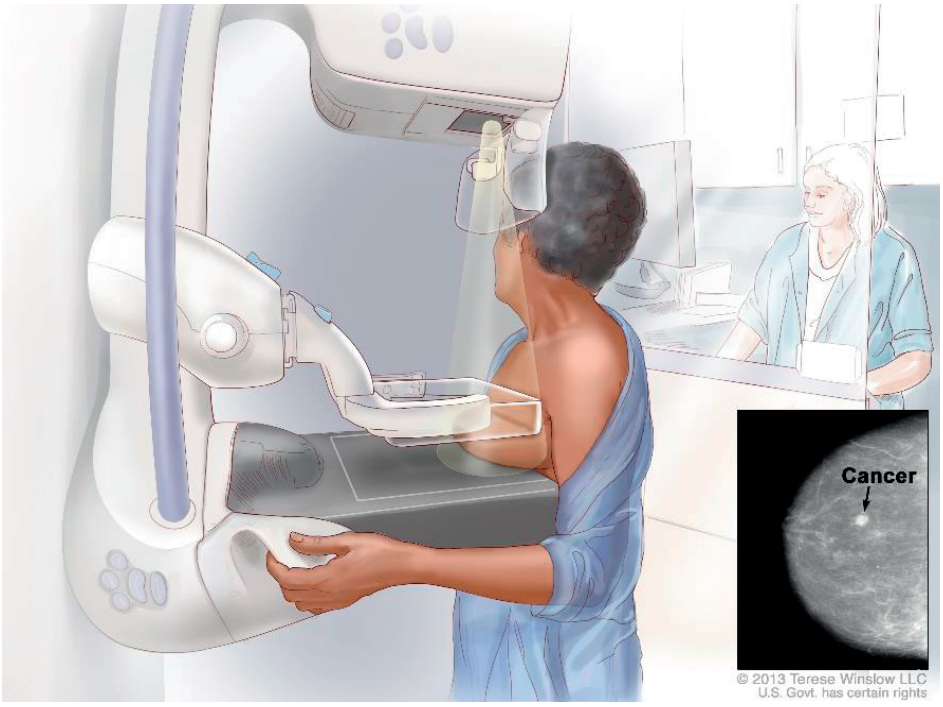

Figure 2 Breast cancer screening examination

Benefits

Breast cancer screening programmes have been designed with the aim to detect breast cancers in early stages allowing for better treatment and a decrease in breast cancer mortality. The first countries implemented breast cancer screening programmes in the late 1980s and since then many western countries have followed.[23] Over time, many trials and observational studies have been performed to see if the aim of the screening programmes was met. A meta-analysis of ten randomised controlled trials (RCTs) of mammography screening showed that screening led to a reduction in breast cancer-specific mortality of about 20%.[25] In addition, observational studies showed that cancers found within the screening programmes were more often of earlier stages and less often late stage.[25-27] Furthermore, screen detected breast cancers are more often treated with breast-conserving surgery than clinically detected breast cancers in women who never participated in screening (71% vs. 38%).[27] Therefore, it can be expected that women with a screen-detected breast cancer will have a higher quality of life than women with a clinically detected cancer.

Harms

Next to the benefits, cancer screening also leads to harms. The most occurring harm in breast cancer screening is a false-positive (FP) result. A FP result occurs when a women is referred for further investigation by the screening programme, but no breast cancer was diagnosed at follow-up. This may cause short-term distress and anxiety in the women due to a fear of having cancer and additional tests being performed, but no effect was seen on long-term anxiety.[28] The amount of false-positive results in a screening programme strongly depends on the referral strategy and reading of the radiologists of the specific programme.

Another important harm of breast cancer screening is overdiagnosis. Overdiagnosis occurs when screening finds a tumour which would never have been diagnosed in a situation without screening. Overdiagnosis can occur because some screen-detected DCIS or indolent invasive breast cancers may never present clinically during the woman's lifetime, because of slow growth, no growth, or regression of the lesion.[29] Another situation in which overdiagnosis can occur is if a women dies of another cause before the tumour would have been detected clinically. In general, overdiagnosis occurs most often in older women in whom tumours usually grow slower and who have a shorter life expectancy.[30, 31] Because almost all diagnosed breast cancers are treated, overdiagnosis automatically leads to overtreatment.

Some other harms of breast cancer screening are that a negative screening result can lead to false reassurance and therefore delay the diagnosis of a breast cancer. This can occur if a women is less aware of or neglects breast cancer symptoms that may occur between screening rounds, because the screening results were negative. However, the screening result could be false negative (i.e. the result is negative, while the woman does have breast cancer). Fortunately, false reassurance was found to, at most, play a minor role in breast cancer screening in the Netherlands.[36] Furthermore, due to the use of radiation with mammography, breast cancer screening can lead to radiation induced breast cancers. However, since the small amount of radiation used, the amount of breast cancers induced, and specifically the amount of additional breast cancer deaths is negligible compared to the amount of lives saved with screening.[37]

Harm-benefit balance

Breast cancer screening programmes are designed in a way to balance the harms and benefits. For example, screening programmes may aim for a certain recall rate which lead to a high detection rate, while keeping the FP rate as low as possible. Increasing the recall rate, can increase the detection rate and may decrease interval cancers, but at a cost of an increase in FP rate and possibly an increase in overdiagnosis as well.[38] Where the perfect

balance is, is subject of discussion. Researchers and policy makers from across the world have different perspectives on this based on, among others, the weight of importance they attribute to the benefits and harms which is reflected in differences in international guidelines and in the way screening programmes are designed between countries and regions.[39-41]

Another point of discussion is the strength of the evidence on the effectiveness of breast cancer screening and the estimated size of overdiagnosis. Some studies questione whether the decrease in mortality seen after implementation of breast cancer screening was the effect of breast cancer screening.[42-44] These studies concluded that the observed reductions in mortality are due to changes in risk factors and improvements in treatment. However, these studies assumed cancer incidence to be static over time which is highly unlikely due to increases in risk factors like obesity, hormone replacement therapy and an increasing age at first pregnancy.[45-47] A modelling study by de Gelder et al. did take an increase in incidence into account and found that, the breast-cancer mortality rate reduction attributable to adjuvant therapy was 15,3% and the mortality rate reduction attributable to screening (in presence of adjuvant therapy) was 20.9%.[20]

In addition, Estimates on the size of overdiagnosis differ largely between studies (-4 to 54%).[32] Differences between these studies can be explained by differences in breast cancer stages included, definition of overdiagnosis used, calculation method, correction for lead time, changes in underlying incidence, and unscreened population as comparison.[32-35] When correcting for these factors, overdiagnosis was estimated to be between 1 and 10%.[34]

Eligible ages

At the moment, most countries who implemented breast cancer screening invite women in the age range 50 to 69. However, the ECIBC conditionally recommends to broaden this age range based on a growing amount of evidence.

Multiple studies investigated the effectiveness of starting breast cancer screening before age 50 and found it decreased breast cancer deaths in women aged 39-49 by 15% to 40%.[48-50] However, younger women are more likely to have false-positive results and, since the incidence in younger women is lower, the absolute benefit is smaller than in women over 50.[51] Still, the ECIBC determined that there is enough evidence to conditionally recommend biennial or triennial screening for women between the age of 45 and 49.[24]

The ECIBC also conditionally recommends triennial screening for the ages 70 to 74. The main harm increasing with screening older women is overdiagnosis and therefore overtreatment. However, the potential amount of overdiagnoses with screening older ages

differs between countries depending on life expectancy and co-morbidity. In populations with a higher life expectancy, the increase in overdiagnosis due to an extended stopping age will probably be smaller than in population with a shorter life expectancy. Therefore, some organisations recommend to take (individual) life expectancy into account when determining a stopping age.[52]

BREAST CANCER SCREENING IN THE NETHERLANDS

The Netherlands was among the first countries to start implementing a population based screening programme for breast cancer. After some local pilots in the 1970s and 1980s, the national roll-out started in 1989 and was completed in 1997.[53] Originally, screen-film mammography was used to screen women between the age of 50 and 69 biennially. However, since 1998 the upper age limit was extended to also include women between the age of 70 and 74. Furthermore, between 2004 and 2010 screen-film mammography was gradually replaced by digital mammography. During this same time period, 2-view mammograms (cranial-caudal and mediolateral-oblique) became the standard for both initial and subsequent screens over 1-view mammograms (only mediolateral-oblique).

During the screening process, women get their screening invitation by mail accompanied by an information folder. Participation is voluntary so women can decide for themselves if they want to participate or not. There is also an option to opt out for all future screening rounds to come. Women who do want to participate can go to the local screening unit where two-view mammography is performed for each breast. These mammograms are assessed by two independent radiologists who are specifically trained to read screening mammograms. Following this assessment, the women receive the test results per mail indicating either 1) no indication of breast cancer found (BI-RADS 1 or 2) or 2) not enough information (BI-RADS 0) or 3) abnormal finding that requires further examination (BI-RADS 4 or 5). In case of the latter two categories, women are referred to the hospital for further testing for the presence of breast cancer.

Yearly, around 1.3 million women are invited for breast cancer screening in the Netherlands (table 1) . Among them, 76% participates which comes down to around 1 million women per year. However, recently the participation rate slowly decreased. The detection rate is 0.69%, which means that around 6,500 women are detected with breast cancer within the screening programme every year. It is estimated that the national screening programme prevents 1000 breast cancer deaths per year, increasing in the coming years.[27] Furthermore, women with breast cancer detected during screening often have a better quality of life than women with breast cancer detected outside of screening.[54]

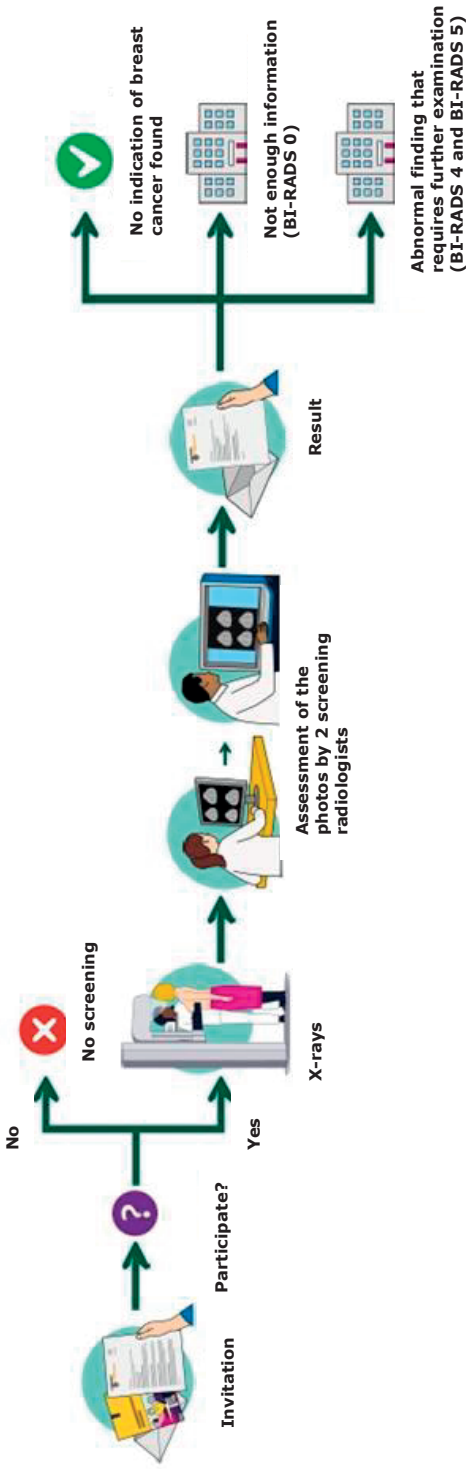

Figure 3 Breast cancer screening process [1]

Table 1 Characteristics of the Dutch cancer screening programmes for breast, cervical, and colorectal cancer

	Breast cancer screening[55, 56]	**Cervical cancer screening**[3, 56-58]	**Colorectal cancer screening**[56, 59, 60]
Eligible population	Women aged 50-75	Women aged 30-60	Everyone aged 55-75
Population invited	1,310,693	807,629	2,192,937
Participation rate	76.0%	56.0%	71.8%
Detection rate	0.69%	1.1%	1.4%
False positive rate	1.7%	2.4%[†]	2.9%[†]
Annual mortality reduction	1000	250	2,250*
Cancers prevented	NA	900	2,600*

* predicted amount in 2030 (when the programme reaches a steady state after implementation)
[†] Calculated by subtracting the detection rate (CIN 2+, and colorectal cancer and/or advanced adenoma) from the referral rate.

It is important to weigh the harms of screening against the benefits and only implement or maintain a programme in which the benefits outweigh the harms. Policy makers analyse this harm-benefit balance on a population level; however, because screening participation is voluntary, women invited for screening make their own personal harm-benefit balance to determine whether they want to participate or not. Preferably, a decision on screening participation is an informed choice (i.e. when a decision is made based on sufficient knowledge and the attitude corresponds with the behaviour). In recent years, participation to breast cancer screening slowly, but steadily decreased from 82.4% in 2007 to 76.0% in 2019.[27, 55] This may indicate that women more often value their personal harm-benefit balance to be unfavourable. However, it is still uncertain whether this is because for example their value or knowledge of benefits decreased, value or knowledge of harms increased, interest decreased, or logistical barriers increased.

OTHER CANCER SCREENING PROGRAMMES IN THE NETHERLANDS

At the moment, the Netherlands has two other cancer screening programmes implemented next to the breast cancer screening programme. These programmes screen for other common cancers in the Netherlands: cervical and colorectal cancer.

Cervical cancer screening

Women between the ages of 30 and 60 are invited for cervical cancer screening every five years. The cervical cancer screening test consists of a cervical swab taken by the general practitioner or via a self-sampling kit. These swabs are tested on the presence of high risk Human Papillomavirus (hrHPV) and in the case of a positive test also on cytology. Clinical follow-up consists of colposcopy during which cervical cancer can be detected, but also

pre-cancerous lesions. These pre-cancerous lesions can directly be removed during the colposcopy procedure which prevents the lesion to grow into cancer. Therefore, the cervical cancer screening programme does not only reduce cancer-specific mortality, but also prevents cervical cancers from developing.[58, 61] Information on the invited population and the programme statistics can be found in table 1.

Colorectal cancer screening

The colorectal cancer screening programme was more recently implemented in the Netherlands. In 2014, the roll-out started to invite all men and women between the age of 55 and 75 for a Faecal Immunochemical Test (FIT) biennially. Since 2018, the roll-out was completed and the entire eligible population was invited. For the FIT, the participants need to collect a small sample of stool with the test kit that was send to their home. Participants for whom blood was detected in the stool above a certain threshold are followed up with a colonoscopy. During colonoscopy, colorectal cancer and pre-cancerous lesions (i.e. polyps) can be detected and pre-cancerous lesions can directly be removed. Therefore, also colorectal cancer screening reduces cancer-specific mortality and prevents colorectal cancers from developing.[60] Information on the invited population and the programme statistics can be found in table 1.

COVID-19 pandemic

Due to the COVID-19 pandemic, all three cancer screening programmes were disrupted for a few months starting March 16th 2020. Once screening was restarted, still some measures were in place to prevent infection which disabled the screening programmes from reaching its full capacity (mainly in breast and cervical cancer screening). Next to that, people were more hesitant to seek help in case they had symptoms of cancer. The combination of these two led to a decrease in cancers detected in 2020 (see figure 1A).[3, 15]

MONITORING AND EVALUATION

Monitoring

The performance of the breast cancer screening programme was monitored yearly by the Netherlands comprehensive cancer organisation (IKNL) until 2022, and since 2023 by the Erasmus MC using performance indicators like participation rate, detection rate, interval cancer rate, FP rate and timing of invitations and results. In the monitor these indicators are reported per calendar year and compared to the data from recent years. The data needed to calculate these indicators are provided by the Netherlands Cancer Registry (NKR). In this registry, interval cancers are defined as cancers detected between two screening rounds

(after a negative screen result). For a positive benefit-harm ratio, it is beneficial to have a relatively high detection rate and a relatively low interval cancer rate and FP rate.

Evaluation

In addition to the yearly monitors, the national evaluation team for breast cancer screening (NETB) evaluates the screening programme to analyse the impact of the screening programme as a whole. Generally, the evaluation consists of observational and modelling studies.

Observational studies

In the observational studies, data gathered on screening invitations, participation, and results, cancer diagnosis, stage, treatment, and mortality, and demographics are used to evaluate the performance of the programme (e.g. patterns in participation, determining factors for referral etc.). These data are usually gathered by the Dutch national registry for screening (ScreenIT) and the Netherlands Cancer Registry (NKR) which is managed by the comprehensive cancer organisation Netherlands (IKNL) and transferred to the NETB for analyses. The cancer screening evaluation data registry works via an opt out system for informed consent. This means that if people choose to participate in screening, they automatically give informed consent to use their data for evaluation purposes unless they explicitly withdraw their consent. Since only a small proportion withdraws their consent, the ScreenIT and NKR databases include data from nearly everyone who participated in cancer screening. Therefore, these data are very representative for the general Dutch screen population which makes it very valuable for evaluation research.

Next to the registry data from ScreenIT and IKNL, also sometimes new observational data is gathered in cohort studies. These studies aim to evaluate outcomes like quality of life and screening knowledge and informed choice of which no data is available in the ScreenIT and IKNL registries.

Improvements

Next to the evaluation of the current breast cancer screening programme, the NETB also investigates the effects of potential improvements to the programme.

Clinical trials

In order to find out if potential improvements have the wanted or expected effect, RCTs can be performed in which the effects of the improvement can be analysed. However, due to ethical reasons it is not always possible to perform an RCT in a screening setting. In that case, a non-randomised clinical trial or a pilot study can be done to still get an indication of the performance of the potential improvement.

Modelling studies

When estimates on effectiveness of potential improvements are known, modelling studies can be used to evaluate what this means in the long term, for different populations, or in different situations. In this thesis, the Microsimulation Screening Analysis (MISCAN) Breast model was used to predict incidence, mortality, quality of life, and cost-effectiveness of an extensive set of screening strategies. In addition, in chapter 3, also the MISCAN-Cervix and MISCAN-Colon models were used.

The MISCAN-Breast model simulates individual natural life histories of a population of Dutch women from birth to death. In a proportion of these women, also the natural history of breast cancer is simulated. In this way, the model can simulate how many women develop breast cancer, at which age, when symptoms cause the cancer to become clinically diagnosed, and whether and when the women recovers or dies from breast cancer. On top of that, the model can simulate one or more specific breast cancer screening programmes. By running the model with and without the screening programme, it can be estimated which cancers can be detected earlier due to the screening and if earlier treatment can improve survival, benefit and quality of life. By comparing the outcomes of the two model runs, the effect of the screening programme can be estimated. Also, by running the model for multiple different screening programme policies, the differences in outcomes between these policies can be estimated.

The MISCAN model has been well reported and validated in the past and is frequently recalibrated and updated with new data.

Cost-effectiveness

A cost-effectiveness analysis (CEA) is an instrument to analyse the harm-benefit ratio of a new policy, policy adjustment, or intervention. With a CEA, the benefits can be weighed against the harms to evaluate whether the investigated policy or intervention is worth implementing. Benefits can be measured in cancer mortality reduction, but also in life years gained (LYG) or quality-adjusted life years (QALYs). When using QALYs, also disutilities for harm can be taken into account. Using data on QALYs and costs for different strategies, an incremental cost effectiveness ratio (ICER) can be calculated which represents the additional costs per additional QALY that is gained between the compared strategies. ICERs allow for a comparison between different policies, interventions, and even different disease- preventive measures. Many countries (including the Netherlands) try to keep the health care expenditure affordable. They try to do this by using a willingness to pay threshold based on the ICER when deciding whether to implement the policy or not.

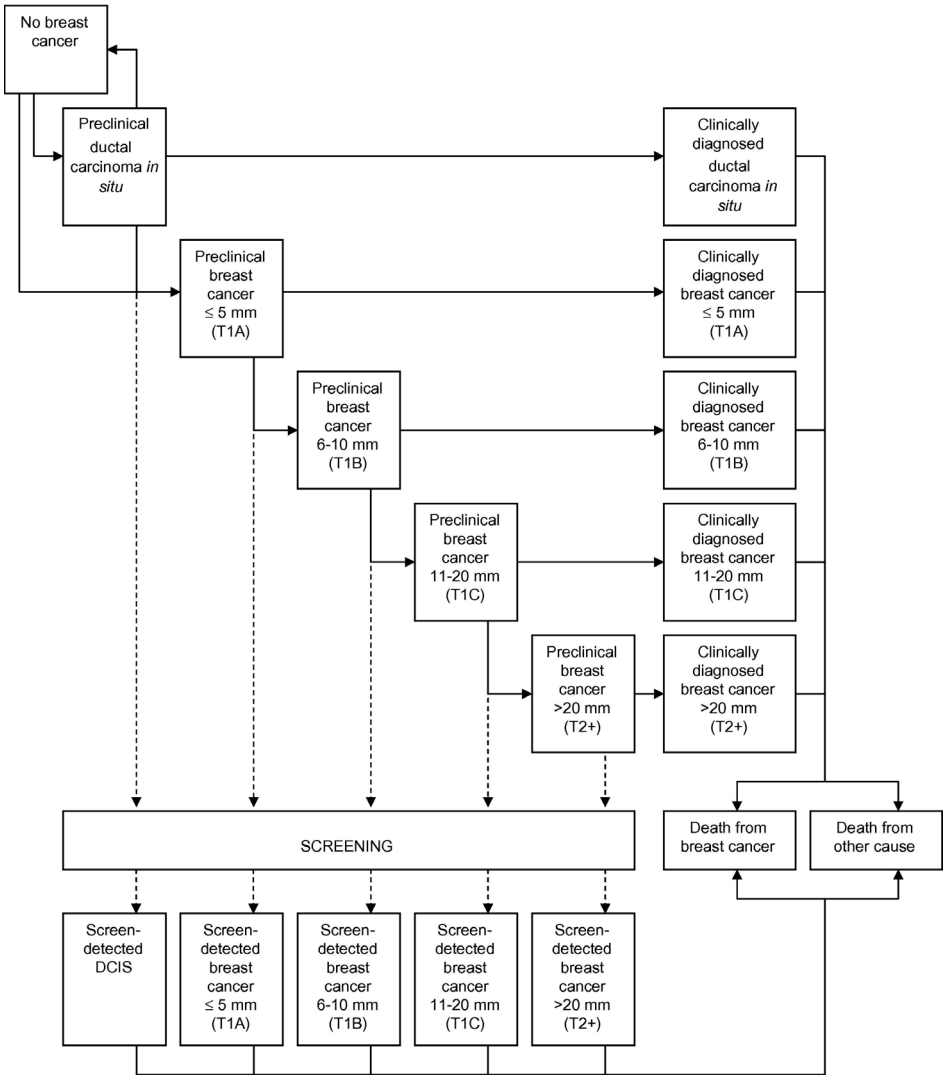

Figure 4 MISCAN Breast tumour grow th, detection, and death transitions [2]

Using the MISCAN-Breast model, the cost-effectiveness of different breast cancer screening policies or potential improvements can be analysed. By providing the cost-effectiveness of these policies and potential improvements, policy makers can be informed about whether or not to implement them.

OUTLINE OF THIS THESIS

The aim of this thesis is to evaluate the Dutch national breast cancer screening programme. This thesis consist of two parts. The first part evaluates the effectiveness of the current breast cancer screening programme in the Netherlands and whether it can be improved. The second part focusses on the perspective of the women eligible for breast cancer screening and their quality of life.

Part 1: Effectiveness of breast cancer screening

In **chapter 2**, we have analysed the effect of breast cancer screening in Europe on the number of breast cancer deaths that are prevented and could additionally be prevented if participation is optimised, for each country separately. In **chapter 3**, the extent to which the participation in breast, cervical, colorectal cancer screening in Dutch women concurs is investigated. On top of that, the chapter looks into factors that potentially influence concurrent participation among these women. **Chapter 4** presents the cumulative risks on a screen detected breast cancer diagnosis and a false positive result when participating in multiple breast cancer screening rounds. In addition, the participation and breast cancer risks of women who previously had a false positive screening result are investigated. **Chapter 5**, focusses on the best way to restart breast, cervical, and colorectal cancer screening programmes after a disruption in the screening programmes. We specifically focussed on the screening disruption caused by the COVID-19 pandemic starting March 2020 which was the first cancer screening disruption affecting many countries at the same time. **Chapter 6**, presents a cost-effectiveness analysis evaluating 920 breast cancer screening strategies differing in starting age, stopping age, and screening interval.

Part 2: Perspectives of the women

In **Chapter 7**, we focus on the effect of the Dutch breast cancer screening information leaflet on screening knowledge, explicit attitudes, and implicit attitudes. Furthermore, the extent to which women make an informed choice about their participation is analysed. In **chapter 8**, normative utilities of a general population of Dutch women are established and compared to international utilities in women. These normative utilities allow for calculations of quality of life lost in diseased women (e.g. women with breast cancer). **Chapter 9** looks into the health related quality of life and accompanying utilities of breast cancer patients stratified by age and treatment options. In addition, the effects of using different normative, breast cancer treatment, and screening and follow-up utility sets in cost-effectiveness analyses is investigated.

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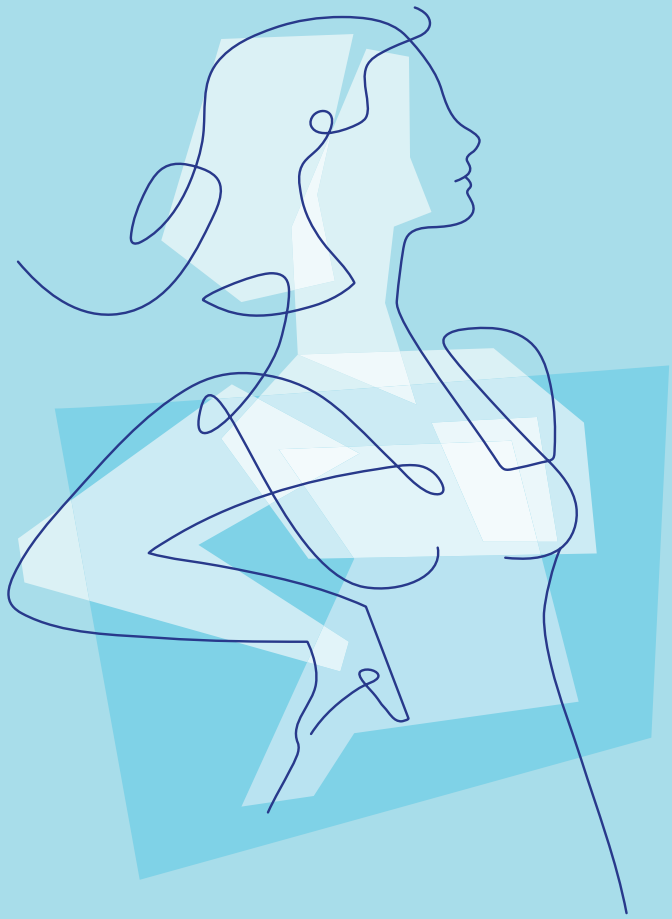
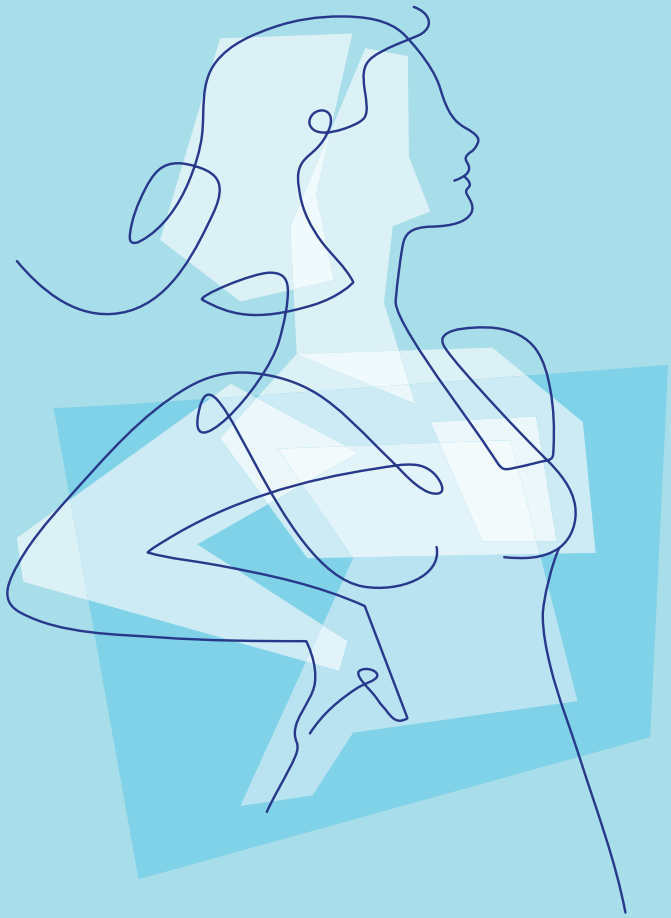


Part 1

Effectiveness of breast cancer screening



2

The potential of breast cancer screening in Europe

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ABSTRACT

Currently, all European countries offer some form of breast cancer screening. Nevertheless, disparities exist in the status of implementation, attendance, and the extent of opportunistic screening. As a result, breast cancer screening has not yet reached its full potential. We examined how many breast cancer deaths could be prevented if all European countries would biennially screen all women aged 50-69 for breast cancer.

We calculated the number of breast cancer deaths already prevented due to screening as well as the number of breast cancer deaths which could be additionally prevented if the total examination coverage (organised plus opportunistic) would reach 100%. The calculations are based on total examination coverage in women aged 50-69, the annual number of breast cancer deaths for women aged 50-74, and the maximal possible mortality reduction from breast cancer, assuming similar effectiveness of organised and opportunistic screening,

The total examination coverage ranged from 49% (East), 62% (West), 64% (North) to 69% (South). Yearly 21,680 breast cancer deaths have already been prevented due to mammography screening. If all countries would reach a 100% examination coverage, 12,434 additional breast cancer deaths could be prevented annually, with the biggest potential in Eastern Europe. With maximum coverage, 23% of their breast cancer deaths could be additionally prevented, while in Western Europe it could be 21%, in Southern Europe 15%, and in Northern Europe 9%.

This study illustrates that by further optimising screening coverage, the number of breast cancer deaths in Europe can be lowered substantially.

INTRODUCTION

Breast cancer is a major public health problem in Europe. It is by far the most frequently diagnosed neoplasm in European women and is responsible for nearly one third of all new cancer cases among women in 31 European countries in 2018.[1] Breast cancer is also the leading cause of death in European women.[1, 2]

Randomised trials and several observational studies have demonstrated that systematic screening of eligible women through quality-assured population-based programmes for breast cancer reduces mortality from this disease.[3-15]

Based on this evidence, in 2003 the European Commission's Initiative on Breast cancer Guidelines Development Group (GDG) published their first guidelines for organised mammography screening programmes for early detection of breast cancer in asymptomatic women with a strong recommendation to inviting women ages 50-69, every two years.[16, 17] The guidelines and recommendations have been updated and expanded regularly ever since based on updated evidence on efficacy or diagnostics, resulting in extending the recommendations to triennial or biennial screening the age-groups 45-49 and 70-74 in the context of an organised screening programme.[17]

At present, breast cancer screening programmes are well established in most European countries and all have some form of screening for breast cancer. Nevertheless, disparities exist in terms of the status of implementation, the extent to which screening programmes are organised, the invitation coverage, the coexistence with opportunistic screening activity and the attendance to screening.[18]

In order to know to which extent the European recommendations have been adopted, reports on the implementation have been published in 2007 and 2017.[3, 18] It was shown here as well as in other studies that the coverage of (organised) screening is of key importance in order to tap the full public health potential in terms of reduction in mortality from breast cancer.[19, 20]

However, in most European countries, opportunistic and organised screening coexist. Thus, to expect mortality reductions only from population-based screening programmes would probably lead to an underestimation of the total effectiveness of screening.

The primary aim of this study was to investigate what the effect would be of an increased or even complete breast cancer screening coverage on breast cancer mortality for each European country and if this effect differs between the four European regions. Therefore,

we estimate how many breast cancer deaths have already been prevented due to screening and how many deaths could additionally be prevented if countries would screen all women in the age-group 50-69 years every two years for breast cancer with a hypothetical 100% coverage of screening in the advised target age groups. The secondary aim was to provide an overview of screening practice and the amount of organised as well as opportunistic screening in Europe.

METHODS

Data

Data providers

As part of the EU-TOPIA project (TOwards imProved screening for breast, cervical and colorectal cancer In All of Europe), we collected data (see indicators listed in this section) of a recent year from over 36 data providers from 31 countries (see list of collaborators). They were either European screening organisers, researchers and/or policymakers. The data providers were contacted to collect any missing data, to correct any apparent inconsistencies and to approve on the use of it. For only a few countries (Greece, Portugal and Romania) data was completely missing despite best efforts of the authors to involve potential data providers. By utilizing other data sources like published reports[3] or online databases (e.g. the Cancer Mortality Database of the WHO[21] or ECIS - European Cancer Information System[22]), we filled these data gaps.

While our focus was clearly on national data, those were not available for a few countries. In Belgium, Spain, Sweden, Switzerland and the UK, healthcare delivery is organised at regional level with effectively independent screening programmes. Therefore, the data for the Belgian regions as well as the data for Scotland, Northern Ireland, England and Wales are presented separately in this study, while the data providers from Spain, Sweden and Switzerland could provide national estimates.

Indicators

Examination coverage of organised screening

Based on the IARC Handbook of Cancer Prevention (2015)[23] we defined organised screening as screening programmes organised at the national or regional level, with an explicit policy, including an active invitation of the entire target population and monitoring of cancer occurrence in the target population. For this study, the examination coverage of organised screening was specified as the proportion (%) of the target population (here: 50-69-year-old women) screened in the chosen report year after invitation. For countries without a population-based programme, the proportion is zero.

Examination coverage of opportunistic screening

Opportunistic or non-organised screening refers to all other breast cancer screening activity where individual invitations are not sent to the women in the eligible population or when women undergo a mammography outside or additionally to the (existing) screening programme.[3, 23] Mammograms for symptomatic women are not counted as opportunistic screening. Generally, opportunistic screening is not monitored and is thus difficult to quantify. We asked the data providers to estimate opportunistic breast cancer screening by utilizing insurance data, survey results or by providing their expert opinion. If that was not possible, we applied the mean examination coverage of opportunistic screening of the European region.

Total examination coverage

We based our calculations on the total examination coverage as the sum of both organised and opportunistic examination coverage. For countries without an organised breast cancer screening programme and no estimate of opportunistic screening, we applied the region-specific average of the total examination coverage.

Breast cancer deaths

We included the absolute number of breast cancer deaths in women aged 50 to 74 years in the report year for each country or region within a country. In addition to the recommended screening ages range 50-69 we included breast cancer deaths for five additional years in ages 70-74 to account for death occurring after the last screening round.

Mortality reduction

The maximal possible mortality reduction is taken from a recently published systematic review on breast cancer mortality reduction due to screening.[7] In this publication, the authors identified those studies among 61 included studies that provided best evidence for breast cancer mortality reduction due to screening for each European region, based on observed data.

The identified studies (Table 1) represent point estimates for breast cancer mortality reduction due to breast cancer screening for each European region. These point estimates were 33% in Finland (North), 50% in Italy (South) and 58% in the Netherlands (West). We assume those reductions to be the same across all screened age groups. No studies from Eastern Europe met the initial inclusion criteria and subsequently evidence for mortality reduction due to breast cancer screening was lacking. Consequently, for these countries we applied the point estimate from Southern Europe as it is the medium value and because these two regions may seem fairly comparable in terms of the extent of screening coverage and the role of opportunistic screening.

Table 1 Overview of point estimates of breast cancer mortality reduction due to breast cancer screening from best evidence studies, per European region

Study	Region	Country	Study type	Target age	Effect size for breast cancer mortality[a], (95% CI)
Heinavaara et al.[9]	North	Finland	Case-control	50-69	HR = 0.67 (0.49-0.90)[b]
Puliti et al.[11]	South	Italy	Case-control	50-74	OR = 0.50 (0.42-0.60)[b]
Paap et al.[12]	West	Netherlands	Case-control	50-75	OR = 0.42 (0.33-0.53)[b]

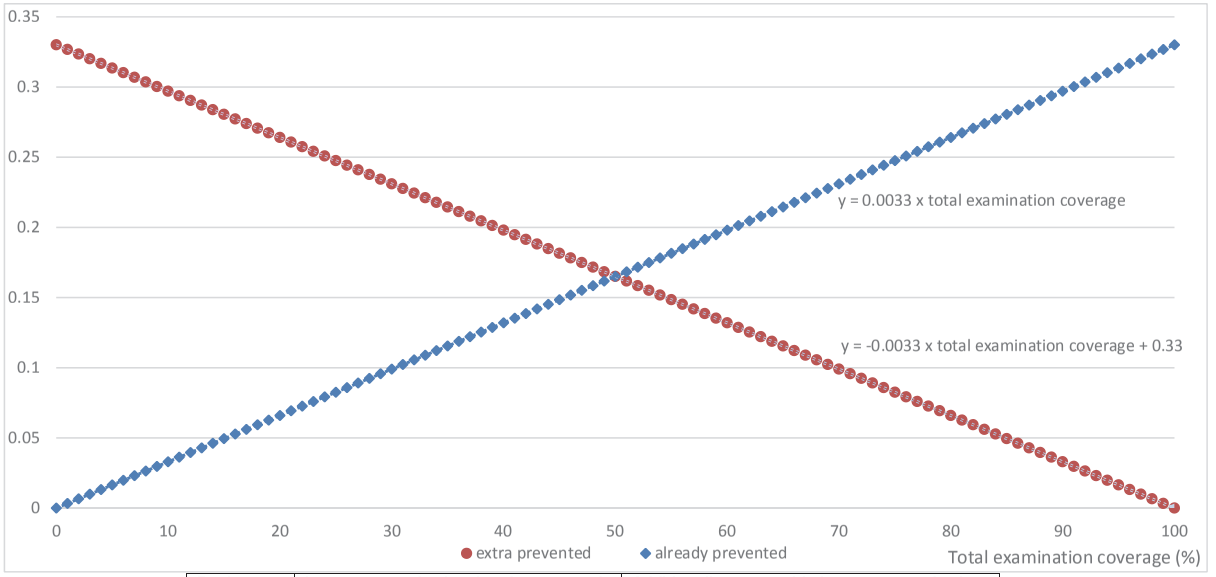
Abbreviations: CI, confidence interval; HR, Hazard ratio; OR odds ratio.
[a] Attenders/non-attenders.
[b] Estimates corrected for self-selection bias.

Calculations

We calculated for each country the number of breast cancer deaths which have already been prevented due to screening as well as the number of breast cancer deaths which could be additionally prevented if the total examination coverage (organised plus opportunistic) would reach 100%, assuming similar effectiveness of organised and opportunistic screening. We made four more assumptions to base our calculations on: first, that the underlying breast cancer mortality between current screening attenders and non-attenders is similar. Second, the maximal effect of breast cancer mortality reduction due to breast cancer screening differs across European regions, but is assumed to be the same in each of the region's countries, respectively. Third, the effects of breast cancer related therapy on the improvement of breast cancer specific mortality are implicitly accounted for in the level of reported breast cancer mortality and possible levels of breast cancer mortality reduction. They are also assumed to be the same in each region. And fourth, that the relationship between examination coverage and breast cancer mortality reduction is a linear one. Through linear interpolation of the point estimates from the best evidence studies for each European region, we were able to assign a potential breast cancer mortality reduction to any level of total screening coverage (calculation examples for each region are in Figure 1).

For example, based on the point estimates of breast cancer mortality reduction due to screening from the best evidence in each region (Table 1), the number of breast cancer deaths that were already prevented in a North European country would be calculated as 0.0033*total examination coverage*annual number of breast cancer deaths of women aged 50-74. For a South and East European country it would be 0.005*total examination coverage*annual number of breast cancer deaths of women aged 50-74 and for a West European country 0.0058*total examination coverage*annual number of breast cancer deaths of women aged 50-74.

Figure 1 (Potential) breast cancer mortality reduction, per total examination coverage (example region North)



Region	breast cancer deaths already prevented	Additionally preventable breast cancer deaths
North	y = 0.0033 * total examination coverage	y = -0.0033 * total examination coverage + 0.33
South	y = 0.005 * total examination coverage	y = -0.005 * total examination coverage + 0.5
West	y = 0.0058 * total examination coverage	y = -0.0058 * total examination coverage + 0.58
East	y = 0.005 * total examination coverage	y = -0.005 * total examination coverage + 0.5

By means of this graph, the number of already prevented breast cancer deaths and additionally preventable breast cancer deaths can be derived for any possible country. The blue line (squares) represents the interpolated trend of the already prevented breast cancer deaths when the maximal possible breast cancer mortality reduction is 33% (Northern Europe). In a hypothetical Northern European country, the total examination coverage is 60% and 3,000 annual breast cancer deaths occur. These deaths need to be multiplied with the value on the y-axis resulting from the respective value on the x-axis (total examination coverage). Or alternatively. 0.0033*60=0.198 and 0.198*3,000=594. Thus, 594 women did not die of breast cancer due to current screening activity. To calculate the corresponding number of breast cancer deaths that could be additionally prevented if the examination coverage would increase to 100%, one needs to calculate the number of breast cancer deaths in the absence of screening first (i.e. the observed number of breast cancer deaths plus the breast cancer deaths that have already been prevented, thus 3,000 plus 594). Based on the total examination coverage, following the red line (circles), one can take the respective factor from the y-axis that these 3,594 deaths need to be multiplied with (or alternatively, y = -0.0033 * total examination coverage + 0.33). Hence, we calculated the factor on the y-axis to be 0.132 (-0.0033*60+0.33) and therefore 474 additional breast cancer deaths could be prevented. For the other three European regions, the calculations should be based on the respective regional values shown in the table above.

In contrast, the breast cancer deaths that could be additionally prevented if the screening coverage would increase to 100% is based on the number of breast cancer deaths in the absence of screening (i.e. the observed number of breast cancer deaths plus the breast cancer deaths that have already been prevented). In a North European country this number would be calculated as (-0.0033* total examination coverage +0.33)* annual number of breast cancer deaths of women aged 50-74 in the absence of screening. For a South and East European country it would be (-0.005* total examination coverage +0.5)* annual number of breast cancer deaths of women aged 50-74 in the absence of screening and for a West European country (-0.0058* total examination coverage +0.58)* annual number of breast cancer deaths of women aged 50-74 in the absence of screening (Figure 1).

Despite differences in target age range and frequency, for this study all calculations were based on the hypothetical situation of a uniform policy of screening women biennially between the ages 50 and 69. The observed coverage rates were adjusted accordingly.

Sensitivity analyses

Because of uncertainties around some assumptions made, the following sensitivity analyses were performed. A sensitivity analysis was performed in which potential gains were calculated up to a maximal coverage of 84%, which is the highest screening coverage found in a European country (i.e. Denmark).

In addition, sensitivity analyses were performed in which the effectiveness of opportunistic screening was 10%, 20%, and 30% lower than organised screening. In these analyses, the percentages that could be gained to reach an examination coverage of 100%, were distributed over organised and opportunistic screening to the same distribution as was already present in the specific country (e.g. if present screening coverage was 40% organised and 20% opportunistic (ratio 2:1), the additional coverage was 27% organised and 13% opportunistic (2:1)).

To assess the impact of the regional point estimates on the maximal possible breast cancer mortality reduction on the regional results of this study, we performed a sensitivity analysis where we varied the point estimates across all European countries, i.e. we applied a 33% (North), a 50% (South) and a 58% (West) breast cancer mortality reduction due to screening irrespective of the location of the country.

RESULTS

Screening practice and Examination coverage

Most European countries adopted the target age range for breast cancer screening as recommended by the European Commission for which there is a strong recommendation (50-69). Only a few countries adopted a different age range and either invite women younger than 50 or they invite women beyond the age of 69, while a few stop inviting women at the age of 62 and 64, respectively. The screening interval was two years in all countries except for Malta and the United Kingdom (UK) where three yearly screening was practiced (Table 2).

The examination coverage of organised breast cancer screening was highest in Northern Europe and lowest in Eastern Europe (an average of 59% compared to 39%, Table 2). In contrast, the examination coverage of opportunistic screening was lowest in Northern Europe and highest in Southern Europe (5% compared to 32%). The total examination coverage ranged from 49% in Eastern Europe, 62% in Western Europe, 64% in Northern Europe to 69% in Southern Europe. With 84% and 25%, Denmark and Switzerland had the highest and the lowest total examination coverage, respectively.

Table 2 Overview of national background data used as input

Country/region	Report year	breast cancer deaths 50-74	Examination coverage 50-69 (%)[1]		
			organised	opportunistic	total
North					
Denmark	2014	521	81.1	3.0	84.1
Estonia[2]	2016	121	37.4	8.0	45.4
Finland	2014	390	78.9	3.9	82.8
Iceland	2015	25	58.7	2.0	60.7
Latvia	2016	247	26.7	8.1	34.8
Lithuania	2016	265	44.2	5.0	49.2
Norway	2016	347	72.3	5.0	77.3
Sweden[3]	2016	605	76.5	1.0	77.5
Total North		*2,521*	*59.5*	*4.5*	*64.0*
West					
Austria[4]	2014	658	25.0	20.0	45.0
Wallonia (B)	2015	386	7.0	45.0	52.0
Brussel (B)	2015	69	11.6	42.0	53.6
Vlaanderen (B)	2015	736	51.0	18.2	69.2
France[3]	2015	5,043	51.6	13.5	65.1
Germany	2015	7,575	51.2	5.0	56.2
Ireland[5]	2015	335	53.3	3.9	57.2

Table 2 Overview of national background data used as input (continued)

Country/region	Report year	breast cancer deaths 50-74	Examination coverage 50-69 (%)[1]		
			organised	opportunistic	total
Luxembourg	2013	29	56.0	5.7	61.7
Netherlands[3]	2015	1,628	75.8	5.0	80.8
Switzerland	2015	616	14.5	10.5	25.0
Scotland (UK)[6, 7]	2015	444	62.1	0	62.1
N. Ireland (UK)[6, 7]	2016	133	81.4	0	81.4
Wales (UK)[6, 7]	2016	264	76.6	0	76.6
England (UK)[6, 7]	4115	4,115	75.4	0	75.4
Total West		*21,972*	*49.0*	*12.1*	*61.5*
East					
Bulgaria	2015	711	-	49.0	49.0[8]
Croatia	2015	533	37.5	12.0	49.5
Czech Republic[4]	2016	823	57.6	3.0	60.6
Hungary[9*]	2015	1,197	22.5	19.5	42.0
Poland	2016	3,421	38.7	19.9	58.6
Romania[10]	2016	1,867	-	49.0	49.0[8]
Slovakia	2017	542	-	30.0	30.0
Slovenia	2015	177	40.1	13.0	53.1
Total East		*9,271*	*39.3*	*16.2*	*49.0*
South					
Cyprus	2017	58	35.1	32.4[11]	63.1
Greece[10]	2016	824	-	*68.9*	*68.9*[8]
Italy	2013	3,900	42.3	19	61.3
Malta[7]	2016	40	52.9	19.5	72.4
Portugal[3, 10]	2013	762	33.8	32.4[11]	66.2
Spain	2016	2,644	62	19.5	81.5
Total South		*8,228*	*45.2*	*32.4*	*68.9*

[1] The examination coverage of organised/ opportunistic screening was specified as the proportion (%) of the target population (here: 50-69 year old women) screened in the index year after invitation.
[2] Screening ages 50-62.
[3] Screening ages 50-74.
[4] Screening ages 45-69.
[5] Screening ages 50-64.
[6] No opportunistic screening activity due to The Ionising Radiation (Medical Exposure) Regulations 2017.
[7] 3-years screening interval.
[8] Total screening is average or the region.
[9] Screening ages 45-64.
[10] Data from ECIS[82], Globocan[81] and the 2nd screening report[64].
[11] Opp. screening is average of the region.

Prevented breast cancer deaths

Based on the collected data, 42,051 women die of breast cancer in Europe every year. Due to the existence of breast cancer screening, 21,680 breast cancer deaths have already been prevented annually. Consequently, with no breast cancer screening activities, 63,731 women would have died of the cancer. Thus, 34% of breast cancer specific deaths have been prevented due to mammography screening across Europe. We calculated that 12,434 breast cancer deaths could additionally be prevented annually if breast cancer screening coverage would be extended to 100%. The regional results are presented in Figure 2 where Western Europe sticks out due to its population size as well as the biggest regional point estimate of breast cancer mortality reduction. In Western Europe, 22,031 women died of breast cancer in the reported year (red column). Due to the average total examination coverage of 61.5%, 13,147 breast cancer deaths were already averted. Hence, in the absence of screening, 35,178 women would have died annually of breast cancer (red striped column). If screening coverage would increase to 100%, only 14,742 breast cancer deaths would occur (grey striped column) as 7,298 additional breast cancer deaths could be averted annually. The respective numbers for all European countries and regions are presented in Table 3.

Figure 2 Annual number of observed and preventable breast cancer deaths, ages 50 to 74, per European region

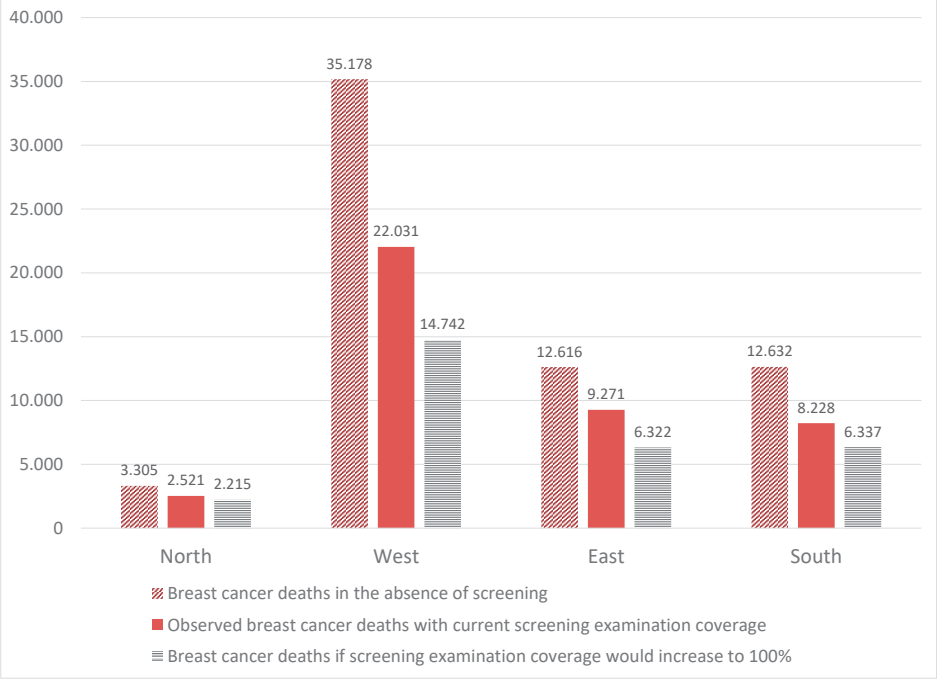


Table 3 Number of (non-)preventable breast cancer deaths, and the results of the sensitivity analysis

	BC death prevented						Sensitivity analysis: Max. European coverage		Sensitivity analysis: Sens -10%[a]	
Region/ Country	A # BC deaths already prevented due to current screening coverage	B # BC deaths prevented if screening coverage would increase to 100	C # BC deaths in the absence of screening	D # BC deaths that cannot be prevented through screening	A/C	B/C	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 84%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%
North										
Denmark	200	38	721	483	28%	5%	200	0	199	38
Estonia	21	26	142	95	15%	18%	21	18	21	25
Finland	147	30	537	360	27%	6%	147	2	146	30
Iceland	6	4	31	21	20%	13%	6	2	6	4
Latvia	32	60	279	187	11%	21%	32	45	31	58
Lithuania	51	53	316	212	16%	17%	51	42	51	53
Norway	119	35	466	312	26%	8%	119	11	117	34
Sweden	208	59	813	546	26%	7%	208	16	209	59
total	784	306	3.305	2.215	24%	9%	784	136	780	301
Comp. base case								*45%*		*98%*
West										
Austria	232	284	890	374	26%	32%	232	201	216	266
Wallonia	167	154	553	232	30%	28%	167	103	147	135
Brussel	31	27	100	42	31%	27%	31	17	28	24
Vlaanderen	493	221	1.229	515	40%	18%	493	107	472	212
France	3.059	1.645	8.102	3.398	38%	20%	3.059	893	3.002	1.600
Germany	3.663	2.868	11.238	4.707	33%	26%	3.663	1.825	3.604	2.827
Ireland	166	125	501	210	33%	25%	166	79	164	124
Luxembourg	16	10	45	19	36%	22%	16	6	16	10
the Netherlands	1.436	338	3.064	1.290	47%	11%	1.436	53	1.424	335
Switzerland	104	313	720	303	15%	44%	104	247	104	296
Scotland	250	153	694	291	36%	22%	249	89	250	138
Northern Ireland	119	28	252	105	47%	11%	119	3	119	25
Wales	211	63	475	201	44%	13%	211	19	211	57
England	3.198	1.060	7.313	3.055	44%	15%	3.198	339	3.198	954
total	13.147	7.289	35.178	14.742	37%	21%	13.146	3.981	12.954	7.003
Comp. base case								*55%*		*96%*

Sensitivity analysis										
Sens. -20%[a]		Sens. -30%[a]		Max West[b]		Max North[b]		Max South[b]	
# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%
198	37	197	37	496	94	200	38	378	72
20	25	20	24	43	52	21	26	36	43
146	30	146	30	360	74	147	30	276	57
6	4	6	4	14	9	6	4	11	7
31	57	31	56	62	117	32	60	52	97
50	52	49	51	106	110	51	53	86	90
116	33	116	33	282	84	119	35	219	65
209	59	208	59	494	140	208	59	383	109
777	297	773	294	1.858	680	784	306	1.440	539
	97%		*96%*		*223%*		*100%*		*176%*
200	250	185	234	232	284	115	140	191	181
129	118	137	107	167	154	80	74	136	125
23	21	22	19	31	27	15	13	25	22
454	203	438	195	493	221	218	98	389	174
2.711	1.511	2.665	1.471	3.059	1.645	1.380	742	2.434	1.308
3.562	2.790	3.523	2.755	3.663	2.868	1.725	1.350	2.960	2.318
163	122	161	121	166	125	78	59	134	101
16	10	16	10	16	10	7	5	13	8
1.411	331	1.400	328	1.436	338	592	139	1.104	259
99	281	95	267	104	313	55	166	88	264
250	122	250	107	250	153	114	70	200	122
119	22	119	19	119	28	49	11	91	21
211	51	211	44	211	63	89	27	164	49
3.198	848	3.198	742	3.198	1.060	1.363	452	2.490	826
12.545	6.682	12.421	6.420	13.147	7.289	5.880	3.345	10.419	5.779
	92%		*88%*		*100%*		*46%*		*79%*

Table 3 Number of (non-)preventable breast cancer deaths, and the results of the sensitivity analysis (continued)

	BC death prevented						Sensitivity analysis: Max. European coverage		Sensitivity analysis: Sens -10%[a]	
Region/ Country	A # BC deaths already prevented due to current screening coverage	B # BC deaths prevented if screening coverage would increase to 100	C # BC deaths in the absence of screening	D # BC deaths that cannot be prevented through screening	A/C	B/C	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 84%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%
East										
Bulgaria	231	240	942	471	24%	26%	231	160	201	205
Croatia	175	177	708	356	25%	25%	175	120	172	172
Czech Republic	358	230	1.181	593	30%	20%	358	136	358	229
Hungary	318	439	1.515	758	21%	29%	318	318	307	416
Poland	1.418	992	4.839	2.429	29%	21%	1.418	605	1.436	962
Romania	605	630	2.472	1.237	24%	26%	605	420	650	566
Slovakia	176	183	718	359	24%	26%	176	194	96	201
Slovenia	64	57	241	120	27%	24%	64	14	74	56
total	3.345	2.949	12.616	6.322	27%	23%	3.345	1.968	3.293	2.807
Comp. base case								*67%*		*95%*
South										
Cyprus	29	14	87	44	33%	17%	29	9	27	15
Greece	433	176	1.257	648	34%	14%	433	75	387	153
Italy	1.724	1.097	5.624	2.803	31%	20%	1.724	647	1.641	1.047
Malta	23	9	63	31	36%	14%	23	10	22	8
Portugal	377	194	1.139	568	33%	17%	377	103	312	173
Spain	1.818	402	4.462	2.242	41%	9%	1.818	45	1.239	342
total	4.404	1.891	12.632	6.337	35%	15%	4.404	888	3.629	1.738
Comp. base case								*47%*		*92%*
ALL	**21.680**	**12.434**	**63.731**	29.617	34	20	21.680	**6.973**	20.657	**11.849**
Comp. base case							*100%*	*56%*	*95%*	*95%*

Abbreviation: BC, breast cancer.

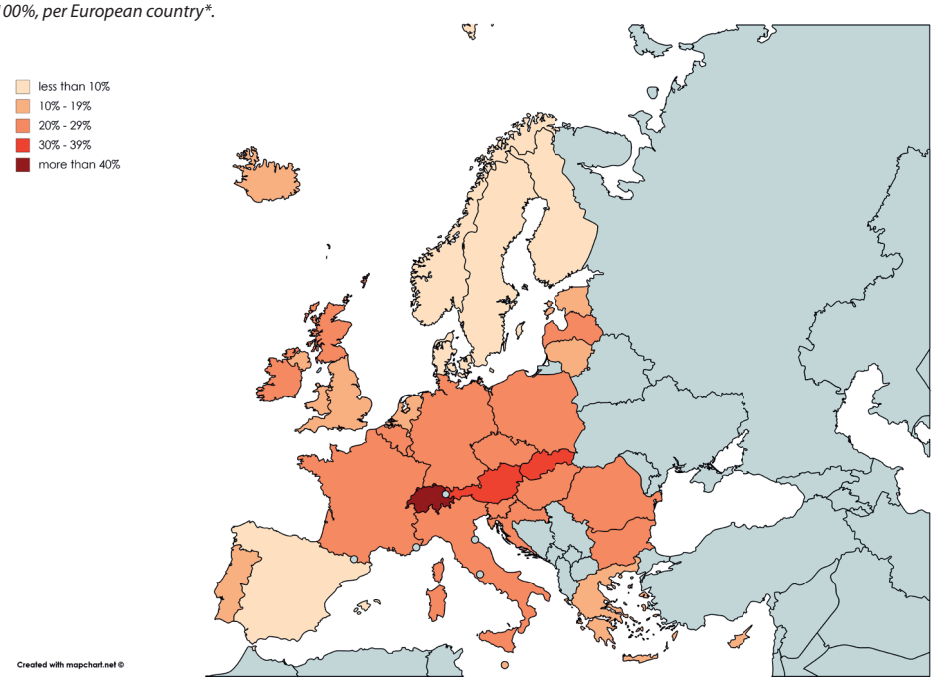
[a] Effectiveness of opportunistic screening to lower cancer specific mortality was set to be 10%, 20% and 30% lower than organised screening. In these analyses, the gained percentages of screening coverage (up to 100%) were distributed over organised and opportunistic screening to the same distribution as was already present in the specific country [eg, if present screening coverage was 40% organised and 20% opportunistic (ratio 2:1), the additional coverage was 27% organised and 13% opportunistic (2:1)].

[b] Application of each of the regional point estimates across all European countries, that is, we applied a 58% (West), a 33% (North) and a 50% (South) breast cancer mortality reduction due to screening irrespective of the location of the country.

Sensitivity analysis										
Sens. -20%[a]		Sens. -30%[a]		Max West[b]		Max North[b]		Max South[b]	
# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%
173	177	193	158	282	288	137	140	231	235
166	166	162	161	215	217	104	105	175	177
355	227	353	226	446	287	206	132	358	230
304	395	301	374	385	532	193	266	318	439
1.370	915	1.309	870	1.761	1.232	820	574	1.418	992
543	482	448	405	741	756	360	367	605	618
83	175	70	150	114	263	60	137	96	220
71	54	69	52	79	70	38	33	64	57
3.065	2.592	2.905	2.397	4.023	3.645	1.917	1.755	3.264	2.969
	88%		*81%*		*124%*		*60%*		*101%*
25	14	25	13	37	20	16	9	29	16
328	129	274	108	549	223	243	99	433	176
1.574	1.002	1.511	958	2.152	1.369	989	629	1.724	1.097
21	8	20	8	29	11	13	5	23	9
293	161	275	150	475	244	213	109	377	194
1.205	331	1.171	320	2.370	523	973	215	1.818	402
3.445	1.645	3.276	1.556	5.611	2.391	2.446	1.066	4.404	1.893
	87%		*82%*		*126%*		*56%*		*100%*
19.832	**11.215**	19.375	**10.667**	24.639	**14.005**	11.028	**6.472**	19.528	**11.180**
91%	*90%*	*89%*	*86%*	*114%*	*113%*	*51%*	*52%*	*90%*	*90%*

Figure 3 presents the relative effect of a 100% total examination coverage for each country, i.e. showing the share of breast cancer deaths that could additionally be prevented when countries would screen all women 50 to 69 years of age every two years. Most countries could potentially avert additional 20%-29% of their breast cancer deaths. In contrast, all Nordic countries have consistently high coverage rates through their organised programmes and less additional breast cancer deaths could potentially be prevented when screening would be extended to 100%.

Figure 3 Percentage of breast cancer deaths that could be additionally prevented if examination coverage would increase to 100%, per European country.*



**Belgium is depicted as one country whereas in the calculation three highly autonomous regions Flanders, Wallonia and Brussels are included. These regions have very disparate screening programs for breast cancer (see Table 2) resulting in very different effects of an increased total examination coverage (Table 3). Only 8 of the 26 Swiss cantons have organised breast cancer screening programmes which causes substantial variation in the distribution of organised vs opportunistic screening across regions. On a national level, total examination coverage was only 25% in 2015 (14% organised and 11% opportunistic) according to the national expert. Thus, a national examination coverage of 100% would further reduce breast cancer deaths by 44%*

Sensitivity analyses

As shown in Table 3, assuming a maximal coverage of 84% instead of 100% led to a significant drop in prevented breast cancer deaths (6,975 averted deaths compared to 12,438). This cut is predominantly explained by countries who already have a comparably high screening coverage and lose the additional benefit of increasing up to 100% (e.g. the Netherlands, Spain or Denmark).

Assuming that opportunistic screening is 10% less effective as organised screening led to a 5% reduction of the additionally preventable breast cancer deaths. A 20% and 30% lowered effectiveness led to a 10% and 14% reduction, respectively. The effect was biggest in countries with a high percentage of opportunistic screening (e.g. Wallonia/Belgium).

Applying the Western European point estimate for mortality reduction across all of Europe, breast cancer deaths already prevented increased by 14% and breast cancer deaths that can additionally be prevented increased by 13%. This analysis has the biggest impact for Northern Europe (plus 223%), where the point estimate was the smallest in the base analysis. When the estimates from Northern and Southern Europe were applied, the number of breast cancer deaths prevented decreased by 49% and 10%, while the additionally preventable breast cancer deaths decreased by 48% and 10%, respectively, compared to the base calculation.

DISCUSSION

This study illustrates how breast cancer screening in Europe already has a substantial impact by preventing nearly 21,700 breast cancer deaths per year. In addition, through further optimising screening coverage, the number of breast cancer deaths of European women could be further reduced significantly. The effect would be particularly notable in Eastern and Western Europe. Thus, rolling-out a breast cancer screening programme with complete coverage across the country is particularly favourable for Swiss women as it would further reduce breast cancer deaths by 44%. In contrast, all Nordic countries have consistently high coverage rates through their organised programmes (between 72% and 81%) plus a very low coverage of opportunistic screening for breast cancer (between 1% and 5%). When the total examination coverage for women aged 50-69 is already as high as 84%, not many additional breast cancer deaths could potentially be prevented if screening was extended to 100%.

Screening provides both harms and benefits, and therefore it is important to ensure a good balance between the two. Information on the balances of benefits and harms is needed to demonstrate that a chosen screening policy and programme with all its components and protocols is appropriate for any given country. In this paper, however, we focus solely on the primary aim of (organised) breast screening which is to reduce mortality from breast cancer through early detection.[16, 20]

The calculations for this present analysis are based on the assumption that opportunistic and organised breast cancer screening can lead to the same level of cancer specific

mortality reduction. However, past studies resulted in slightly conflictive results. For example, a study in Denmark found that the sensitivity was twice as high for organised screening, while the specificity of organised and opportunistic screening was found to be similar.[24] Hofvind et al. compared opportunistic breast cancer screening in Vermont (USA) with organised breast cancer screening in Norway.[25] Both screening systems detected cancer at about the same rate and at the same prognostic stage. A study from Switzerland found that there was little difference in stage distribution and detection rates between cantons with only opportunistic screening and cantons with both organised and opportunistic screening[26], indicating that both are similarly effective. It was noted however that the quality of opportunistic screening in Switzerland probably benefitted from the training of radiographers, a higher reading volume of radiologists and the technical and quality-controlled procedures of the organised programme.

In summary, the main differences between organised and opportunistic screening can be seen in attendance[27], equity[27], and cost-effectiveness[28] which are all (much) better in organised screening. With regards to quality aspects, opportunistic screening might be quite similar to that of organised screening. Moreover, since opportunistic screening takes place next to organised screening in most countries (Bulgaria, Romania, Slovakia and Greece being the exception), it can profit from advantages of the organised system. Consequently, we are confident that by conflating opportunistic and organised screening for calculations and argumentations, we can increase the relevance of this paper.

The European guidelines for quality assurance in breast cancer screening and diagnosis consider participation rates above 70% as acceptable and above 75% as desirable.[29] In line with those guidelines, we do not actually propagate a screening coverage of 100% as this probably conflicts with informed choice.[30] However, by basing our calculations on a hypothetical goal of a screening coverage of 100% of eligible women, we assessed the maximum potential of breast cancer screening for each country.

This study focuses on screening women ages 50-69 as this is currently the practice in most European countries. Despite some exceptions (Table 2), women aged 70–74 are usually not eligible for mammography screening because there was insufficient evidence that screening would reduce mortality for women in this age group. Previous randomized controlled trials (RCTs) and observational studies on breast cancer screening have not generally included women aged 70 years and over. In their newest screening (conditional) recommendations, however, the European Commission Initiative on Breast Cancer suggests that average-risk and asymptomatic women between 45 and 49 as well as between 70 and 74 years old, have mammography screening for breast cancer.

Several further considerations inform the interpretation of our study. There is an ongoing debate as to which study design is the gold standard for estimating the true effect of screening on cancer specific mortality.[12, 31, 32] For this study, we considered that high-quality case control studies[7] provide the most informative data. RCTs were conducted more than 20 years ago when adherence to screening was less and the quality of screening programmes and breast cancer care were less advanced than today. In contrast, observational studies of screening are known to be prone to bias as there is no unselected unscreened group. Women who do not participate in screening might have a higher a priori risk of breast cancer mortality. If that was so, our assumption of a proportional relationship between screening coverage and reduction in breast cancer mortality would not hold. Therefore, it was of particular importance to base our analysis on estimates of mortality reduction that were not influenced by self-selection bias.

The regional point estimates from individual studies on mortality reduction due to breast cancer screening, which our calculations are based on, differ quite significantly. These differences indicate differences in evaluation designs, in target ages, in ages of follow-up of breast cancer incidence or mortality, in duration of follow-up since first invitation, in comparison groups, and in assessment methods of self-selection bias.[7, 9, 12, 33] Therefore, the region-specific point estimates are not directly comparable with each other and they should not be used as a "quality indicator" for organized breast cancer screening in each region.

Despite the different effect sizes, we are confident that our three regional estimates do not present an overestimation of the benefit of mammographic screening. They are well in the range of an analysis of Broeders at al. from 2012[5] who present a pooled breast cancer mortality reduction for women who actually participated in screening of 38% based on incidence based mortality studies (OR = 0.62 [0.56-0.69]) and 48% based on case control studies (OR = 0.52 [0.42-0.65], adjusted for self-selection). An analysis similar to this study has been published in 2013. Mackenbach and McKee[34] estimated there would be over 17,000 fewer breast cancer deaths each year if all countries in the EU could reduce death rates to those in the best performing country, Sweden. However, this study was based on cause- and age-specific death rates only rather than the combination of cause- and age-specific mortality and the extent of screening activity.

To our knowledge, there have been no other studies so far that have estimated the effect of breast cancer screening on cancer specific mortality when brought to its full potential based on the total extent of breast cancer screening activities in Europe. We were able to provide an extensive overview of the amount of organised as well as opportunistic

screening in Europe by consulting national experts. Accordingly, some of the national estimates on screening uptake have never been published before.

However, our study also has some potential limitations. The first limitation is the uncertainty regarding the coverage of opportunistic screening as these numbers are based on expert opinion or on national extrapolations of regional observations. Secondly, because the organised breast cancer screening in the UK as well as Malta is triennially rather than every two years, this led to a slight overestimation of the breast cancer death prevented. Third, our calculations probably led to an underestimation of the already prevented and additionally preventable deaths for the few countries which invite and screen women that are younger than 50 or older than 69. The fourth limitation is the fact that the number of breast cancer deaths and the estimates of examination coverage come from the same report year although the most recent breast cancer deaths rather reflect the past (e.g. 5-10 years ago) than current screening practice.

Our analysis paves the way for further research as it could potentially be applied to the other two cancer sites for which the European Council recommends screening: cervical and colorectal cancer.

This study illustrates that by further optimising screening coverage, the number of breast cancer deaths in Europe could be lowered substantially. Therefore, countries which do not yet offer organized screening for the target age range of 50 to 69 should strongly consider it based on our results. In addition, even when programmes to screen for breast cancer exist, much is still to be done. This includes increasing screening coverage through evidence-based interventions[35, 36] and removing barriers to effective breast cancer screening.[37, 38]

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Disclosure

HJDK reports personal fees from the University of Zurich/MSD.

Data accessibility

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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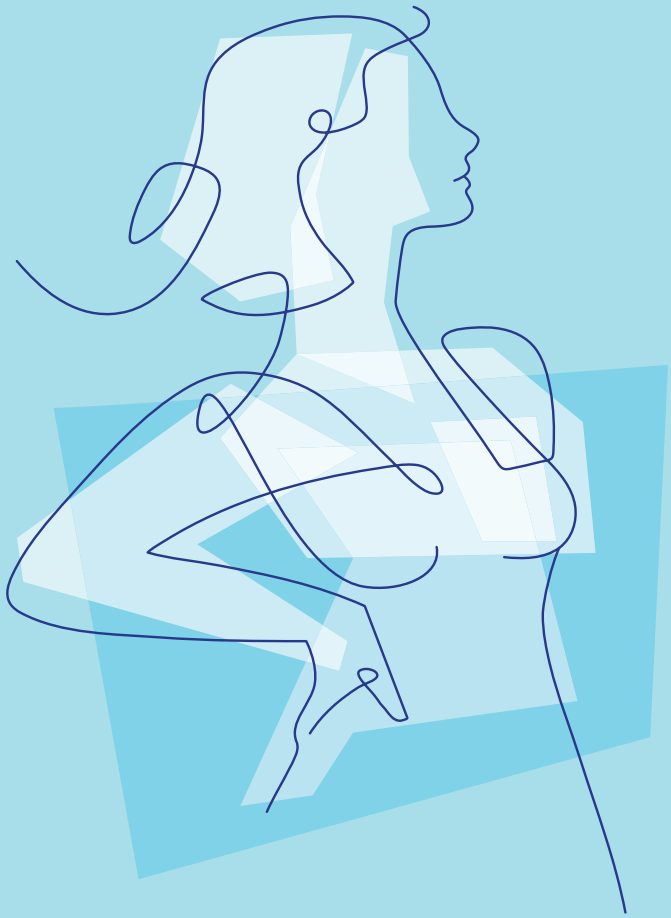

3

Concurrent participation in breast, cervical, and colorectal cancer screening in the Netherlands

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ABSTRACT

Background

Many European countries offer organised population-based breast, cervical, and colorectal cancer screening programmes. Around age 55 and 60, Dutch women are invited to all three screening programmes. We examined the extent to which participation concurs and identified factors influencing concurrent participation.

Materials and methods

Individual level data from breast, cervical, and colorectal cancer screening invitations between 2017 and 2019 were extracted from the Dutch screening registry. The percentages of women participating in all three, two, one, or none of the programmes around age 55 and 60, and before subsequent round invitation were determined. Multivariate ordinal regression analyses were performed to estimate whether population density, socio-economic status (SES) per postal code area, and time between the three invitations (<3, 3-6, >6 months) were associated with concurrent participation.

Results

Data from 332,484 women were analysed. At age 55, 53.7% participated in all three programmes, 22.1% in two, 11.7% in one, and 12.6% did not participate at all. At age 60, a similar participation pattern was observed. Women living in areas with higher population density were less likely (0dds ratios 0.75-0.94) and women in higher SES groups were more likely (odds ratios 1.12-1.60) to participate in more screening programmes, although this positive association was smaller for the highest SES group. No substantial association was found between concurrent participation and timing of invitations.

Conclusions

More than half of Dutch women participated in all three screening programmes and around 12% did not participate in any. Concurrent participation was lower in cities and lower SES groups.

INTRODUCTION

In the European Union (EU), organised screening is recommended for breast, cervical and colorectal cancer and many countries offer organised cancer screening programmes. These three screening programmes have been shown to detect cancers at early stages and can thereby reduce cancer-specific mortality.[1-3] In addition, cervical and colorectal cancer screening detects pre-cancerous lesions, which allows for the treatment of these lesions, thereby preventing cancer from developing.[4,5]

In the Netherlands, participation to the cancer screening programmes is relatively high with 76.0% participating in breast cancer screening, 71.8% in colorectal cancer screening, and a five-year participation coverage rate of 65.2% in cervical cancer screening.[6-8] Various factors have been found to influence participation in cancer screening programmes. For example, in the Netherlands the participation rate is lower among migrants, with the lowest participation in non-western migrants.[9] Because the migrant population is bigger in larger cities, the participation rate there is also lower than average. However, the influence of population density of the place of residence on concurrent participation has not been investigated before. Furthermore, it was shown that participation in breast cancer screening among native Dutch women living in the biggest city (i.e. Amsterdam) was lower than among native Dutch women living in surrounding areas, suggesting that not only migration background plays a role in the lower participation rates in larger cities.[9] Additionally, it has been shown that participation in colorectal and cervical cancer screening is lower among people with a lower socio-economic status (SES).[10,11]

Previous studies in other Western countries have shown that the percentage of women participating in all three programmes around the same time ranges between 26.9% and 52.1%.[12-14] This wide range might be due to differences between screening programmes (e.g. eligible population, invitation procedure, test modality, test location) and screening culture (i.e. health/risk perception, health seeking behaviour, and attitude towards screening opportunities provided by the government of the eligible population).[15-17] Because both the screening programmes and screening culture differ between countries, it is unknown to what extent participation between screening programmes concurs in the Netherlands.

In the Netherlands, at a certain age, women are invited to all three screening programmes. Information about concurrent participation at these ages can provide insights into participation patterns. Understanding participation patterns can be used to increase participation to screening programmes through, for example, offering information about other screening programmes when a woman participates in one of the other programmes.

Therefore, this study aimed to examine the extent to which participation in breast, cervical and colorectal cancer screening concur and to identify factors influencing concurrent participation in the Netherlands.

METHODS

Dutch screening policy

Currently, the Netherlands invites its inhabitants for three cancer screening programmes, breast, cervical and colorectal cancer screening. The breast cancer screening programme invites women aged 50 to 74 every two years for mammography screening. The cervical cancer screening programme invites women aged 30 to 60 every five years for primary high-risk human papillomavirus (hrHPV) screening. In addition, colorectal cancer screening was implemented since 2014 with a roll-out phase until 2019. Both men and women aged 55 to 75 are invited for Faecal Immunochemical Testing (FIT) every two years. This means that Dutch women receive invitations to all three screening programmes around age 55 and around age 60 (Figure 1).

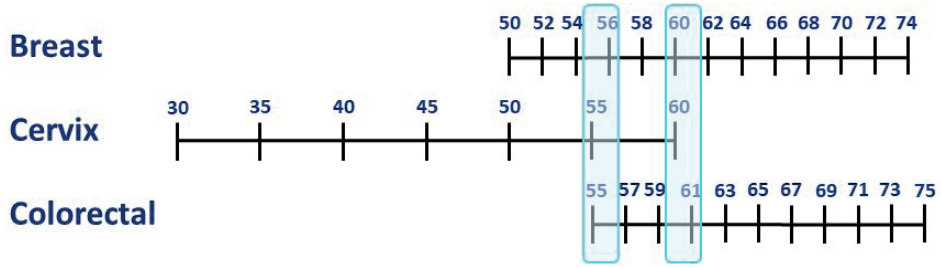

Figure 1. Ages at which Dutch women are invited for breast, cervical, and colorectal cancer screening. The blue boxes represent the ages at which women are invited for all three screening programmes. These are the ages that are included in this study.

Population

This cross-sectional, observational cohort study included all Dutch women who were 55 or 56 (age group 55), and 60 or 61 (age group 60) years old between January 2017 and December 2019 and received screening invitations for all three screening programmes. In the Netherlands, implicit informed consent to pseudonymised data use in research is recorded when one takes up the offer of screening. All individuals were informed that they could explicitly withdraw consent. Furthermore, women who were recently diagnosed with breast, cervical or colorectal cancer or who permanently opted out from one or more programmes and therefore received less than three invitations were excluded from the study.

Data

Screening invitation and participation data from the three cancer screening programmes were retrieved from the Dutch national screening registry (ScreenIT). The data included the date of invitation, participation (Y/N), and date of participation. Furthermore, the data included demographic information including year of birth, place of residence and 4-digit postal code. Data from Statistics Netherlands were used to identify population density based on the place of residence data and median household income based on 4-digit postal code.

Definitions

Participation in a screening programme was defined as the registration of a screening test as part of the national screening programme in ScreenIT after the sending of a screening invitation and before the sending of the invitation of the subsequent screening round. We use the term concurrent participation to mean participation in all three programmes following invitation at the same age. Population density of the place of residence was defined according to the degree of urbanisation set by the World Bank; city: >1500 inhabitants per km^2, town: 300-1500 inhabitants per km^2, and rural: <300 inhabitants per km^2.[18] Second, annual median household income of the postal code area of residence compared to the median Dutch household income in 2018 was used as a proxy for SES.[19] The median household income was divided into five categories indicating a 'low' (<€16,800), 'under median' (€16,800-€22,200), 'median' (€22,200-€28,400), 'over median' (€28,400-€36,600), and 'high' (>€36,600) SES. Furthermore, the effects of a simultaneous screening invitation, during which people receive one screening invitation for multiple screening programmes, were investigated by using the proxy of timing of the receipt of the three different screening invitations. This variable considered three categories; (1) receiving all three invitations within three months, (2) receiving all three invitations between three to six months, and (3) at least two invitations were more than six months apart.

Statistical analyses

The proportion of women in each concurrent participation pattern was presented using descriptive statistics. Multivariate ordinal regression analyses were performed to assess the impact of the independent variables population density, SES and timing of invitations on the dependent variable number of screens attended (i.e. 0, 1, 2 or 3) using an α of 0.05 and a β of 0.8. This resulted in odds ratios (ORs) per category with corresponding 95% confidence intervals (95% CIs). Likelihood ratio tests were performed to test the contribution of each of the independent variables to the regression model. Multicollinearity between the independent variables was tested using a variance inflation factor cut-off of 5. The analyses were performed for both age groups (age 55 and 60) separately. Statistical analyses were performed in IBM SPSS Statistics version 28.

RESULTS

In total, 156,088 women aged 55 and 176,396 women aged 60 were included in the study. Considering participation for each of the programmes separately, around three quarters of the women participated in breast and colorectal cancer screening and around two-third participated in cervical cancer screening at both ages (Table 1). Most women lived in a town (43.4%-44.3%) and had a median annual household income between €22,200 and €28,400 (63.5%-64.5%). At age 55, 16.5% of the women received all three screening invitations within a period of three months, and 25.4% of the women received all three invitations in a period of three to six months. At age 60, nearly all women received the three invitations more than six months apart (99.5%).

Table 1 Population characteristics

	Age 55		Age 60	
	n	%	n	%
Total population	156,088		176,396	
Participation in separate screening programmes (n; % participating)				
Breast	117,051	75.0%	136,950	77.6%
Cervix	104,315	66.8%	117,167	66.4%
Colorectal	116,992	75.0%	132,543	75.1%
Population density of place of residence				
City (>1,500 inhabitants per km^2)	53,233	34.1%	59,515	33.7%
Town (300-1,500 inhabitants per km^2)	67,730	43.4%	78,206	44.3%
Rural (<300 inhabitants per km^2)	34,772	22.3%	38,168	21.6%
Missing	353	0.2%	509	0.3%
Median annual household income of postal code area of residence				
Low (< €16,800)	408	0.3%	563	0.3%
Under median (€16,800 - €22,200)	25,172	16.1%	28,135	15.9%
Median (€22,200 - €28,400)	99,038	63.5%	113,794	64.5%
Over median (€28,400 - €36,600)	30,229	19.4%	32,361	18.3%
High (> €36,600)	672	0.4%	761	0.4%
Missing	569	0.4%	784	0.4%
Timing of the three different screening invitations				
< 3 months	25,680	16.5%	285	0.2%
3-6 months	39,675	25.4%	649	0.4%
> 6 months	90,733	58.1%	175,464	99.5%

Table 2 Concurrent participation divided into the eight participation patterns at age 55 and age 60

Participation	Breast	Cervix	Colorectal	%	
				Age 55	Age 60
3 programmes	x	x	x	53.7%	54.1%
2 programmes	x	x	-	5.3%	5.6%
	x	-	x	10.5%	11.9%
	-	x	x	6.3%	5.2%
1 programme	x	-	-	5.6%	6.1%
	-	x	-	1.6%	1.6%
	-	-	x	4.5%	4.0%
Non-participation	-	-	-	12.6%	11.6%

Of the women who were invited for all three screening programmes, 53.7% of 55-year old women and 54.1% of 60-year old women participated in all three programmes (Table 2). In total, 22.1% and 22.7% participated in two programmes respectively, where participation in breast and colorectal cancer screening was most common. Furthermore, 11.7% of women in both age groups participated in one screening programme, where participation to only cervical cancer screening was the lowest (1.6%). Last, 12.6% and 11.6% of women respectively did not participate in any of the screening programmes (Figure 2).

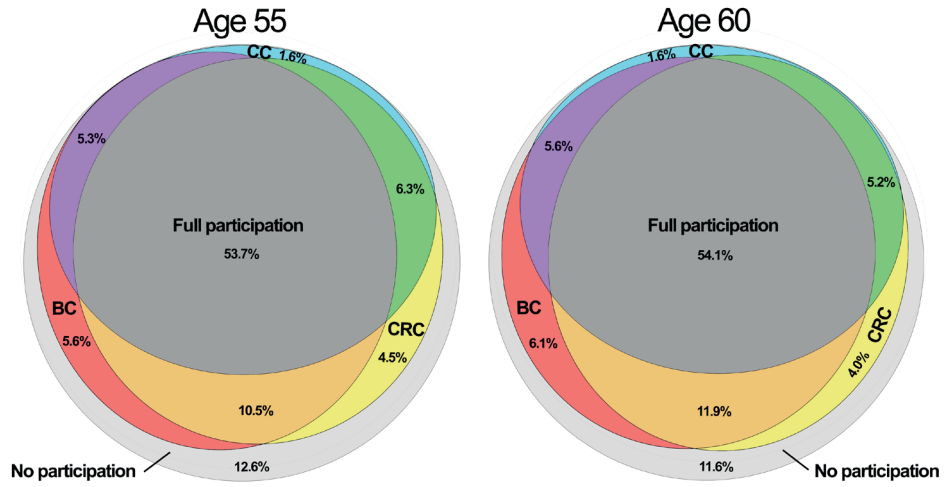

Figure 2 Euler diagrams of concurrent participation for the two age groups. Blue: only cervical cancer, red: only breast cancer, yellow: only colorectal cancer, purple: cervical and breast cancer, green: cervical and colorectal cancer, orange: breast and colorectal cancer, Dark grey: cervical, breast, and colorectal cancer (full participation), light grey: no participation.

The likelihood ratio tests showed that all variables were associated with concurrent participation (p-values<0.001). Multivariate regression analyses showed that women living in a city were less likely to participate in more screening programmes than women

living in a rural area (age 55: OR= 0.75; age 60: OR=0.77) (Table 3). Also women living in a town were less likely to participate in more screening programmes than women living in a rural area (age 55: OR= 0.93; age 60: OR=0.94). Overall, full participation was 47-48% in cities, 56-57% in towns, and 58-59% in rural areas, while non-participation was 16-17% in cities, 10-11% in towns, and 8-9% in rural areas (appendix table 1).

Table 3 Results from the multivariate ordinal regression analyses

	Age 55		Age 60	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Population density (compared to rural)		<0.001*		<0.001*
Town	0.93 (0.92-0.95)		0.94 (0.92-0.95)	
City	0.75 (0.74-0.77)		0.77 (0.76-0.78)	
SES/ household income (compared to low)		<0.001*		<0.001*
Under median	1.12 (1.00-1.25)		1.22 (1.12-1.34)	
Median	1.46 (1.31-1.62)		1.55 (1.42-1.70)	
Over median	1.60 (1.44-1.79)		1.70 (1.55-1.86)	
High	1.35 (1.17-1.55)		1.55 (1.37-1.75)	
Timing of invitations (compared to >6 months)		<0.001*		-
<3 months	0.98 (0.97-0.99)		-	
3-6 months	0.99 (0.97-1.00)		-	

* These variables are statistically significant associated with concurrent participation using the alpha of 0.05

In addition, for both ages, living in an area with a higher median household income was associated with participating in more screening programmes. Women in the 'over median' income group were most likely to participate in most programmes (age 55: OR=1.60, p<0.001; age 60: OR=1.70, p<0.001). An exception, however, was the highest household income group, in which women were more likely to participate than women in the lowest income group, but less likely than women in the 'over median' group (age 55: OR=1.35; age 60: OR=1.55). Full participation ranges between 37-39% in the lowest SES group to 58% in the 'over median' age group, with 50-51% in the highest SES group (appendix table 2). Moreover, non-participation ranged between 21-22% in the lowest SES group to 9-10% in the 'over median' group, with 11-14% in the highest SES group.

The timing of invitations variable was only included in the regression model at age 55, because at age 60, 99.5% of the women received the invitations more than six months apart (Table 1). Women who received the three screening invitations within three months' time and between three to six months were a little less likely to participate in more screening programmes than women who received their invitations more than six months apart (OR=0.98 and OR=0.99, respectively). Even though, the timing of invitations was statistically significant associated with concurrent participation, the OR was so close to 1

that it is likely not relevant for public health. Full participation was 53.2% in the <3 months and 3-6 months groups and 54.0% in the >6 months group, while non-participation was 13% in the <3 months and 3-6 months groups, and 12% in the >6 months group (appendix table 3).

DISCUSSION

This study showed that more than half of Dutch women who received three screening invitations around age 55 and 60 participated in all three cancer screening programmes. Furthermore, 22% participated in two programmes, 12% participated in one programme, and 12% did not participate at all. Living in an area with a higher population density and a lower SES based on median household income were associated with lower odds for participating in more screening programmes. Furthermore, receiving invitations for the different screening programmes in a short time period did not lead to clinically relevant differences in concurrent participation.

Previous studies investigating concurrent participation in breast, cervical, and colorectal cancer screening in other countries found different levels of concurrent participation than our study. The greatest difference was observed between our study and a study in Japan, where the percentage of women participating in all three screening programmes was substantially lower at 26.9%.[12] However, this difference can probably be explained by the differences in screening culture, organisational structure and the share of opportunistic screening, which are also reflected in lower overall participation rates to the separate cancer screening programmes ranging from 40 to 46%.[12] In an English study, although the screening culture and organisation were quite comparable to the Netherlands, concurrent participation was also much lower (35% full participation).[14] The participation to the separate programmes was similar for breast cancer (78%) and cervical cancer (73%) and lower for colorectal cancer (59%). This study showed that women were most hesitant in participating in colorectal cancer screening, possibly due to less user-friendly guaiac Faecal Occult Blood Test (gFOBT) used at the time of the study.[14,17] This resulted in 21% of the women participating in breast and cervical cancer screening, which was only 5.3% in our study. In Scotland, cancer screening is similarly organised as in England; however, concurrent participation in the Scottish study was higher (52.1% full participation).[13] The lowest participation was seen for the colorectal cancer screening programme (62%). However, a high proportion of women who attended breast or cervical cancer screening also participated in colorectal cancer screening (>70%), coming closer to the observed concurrent participation in our study.[13] Apparently, screening organisation and differences in culture have an even larger effect on concurrent participation than they

have on participation to the separate screening programmes. Similar to our study, these three studies on concurrent participation also found lower concurrent participation in lower SES groups.[12-14]

We found that women who received all three invitations within three months were not less likely to participate in multiple screening programmes. Therefore, it is not needed to synchronise the timing of sending the invitations of the separate screening programmes either further apart or closer together. Looking at the effect of the timing of invitations on concurrent participation might give an indication of the effect of sending combined invitations or even combining screening tests during one screening appointment. In this case, it would indicate that offering multiple screening invitations or tests simultaneously does not notably decrease participation across multiple programmes. Although, further research with the intervention of combined invitation and combined testing is needed to investigate whether this is the case.

An important strength of our study is that a large sample of women from the nationwide registry was used, which implied adequate representation of the study population and limited information bias. Furthermore, it was the first study to investigate the effect of population density and timing of invitations on concurrent participation. Next to that, our study also had some limitations. First, the study population may not be completely representative for all women aged 55 and 60 in the Netherlands, because only women who received all three screening invitations were included in the study. Therefore, women who opted out for at least one screening programme and women who were diagnosed with a cancer earlier were not included in the study population, which might have caused a slight underestimation of the proportion of women with partial or no participation. Furthermore, the proxy of median household income of the postal code area of residence used for SES can give an incomplete comparison by downgrading individual SES scores and leaving out the other components of SES like level of education and occupation. Using individual data on the personal SES of the study participants would have led to more accurate estimates, however, was not available for this study due to privacy law enforcement. In addition, by using the median of the area, extreme high and low household incomes averaged each other out, resulting in 65% of the participants being classified in the median SES group. Also, the regression analyses found associations for population density, SES, and timing of invitations on concurrent participation, but did not prove causality. However, the found associations can provide insights for policy makers in which subgroups or communities it is most useful to provide additional screening information. In addition, information about the other screening programmes can be provided to the women with partial participation (33%). This can increase screening knowledge and informed choice and potentially participation to the other screening programmes.

In conclusion, this study found that more than half of the Dutch women aged 55 and 60 participate in all three offered cancer screening programmes, while about 12% does not participate in any screening programme. Lower population density and higher SES were found to be associated with participation in more screening programmes. Timing of the three invitations did not affect concurrent participation.

Conflict of interest

The authors declare no conflict of interest.

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Data availability

The data used in this study are property of the Dutch national screening organisation Bevolkingsonderzoek Nederland and Statistics Netherlands. Data from Statistics Netherlands can be downloaded from their website at https://opendata.cbs.nl/statline/portal.html. Data from Bevolkingsonderzoek Nederland can be requested at Bevolkingsonderzoek Nederland via (wetenschappelijkonderzoek@fsb-ssc.nl).

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APPENDIX

Concurrent participation stratified by population density, SES, and timing of invitations

Appendix Table 1 Concurrent participation stratified by population density

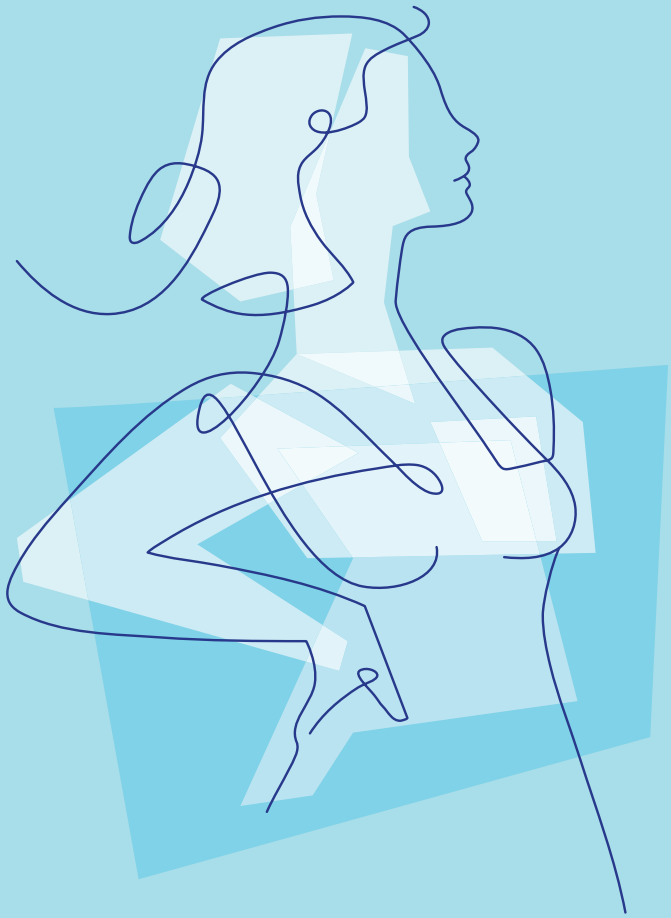
Participation	Breast	Cervix	Colorectal	City		Town		Rural	
				55	60	55	60	55	60
3 programmes	x	x	x	46.5%	47.6%	56.5%	56.3%	59.1%	58.4%
2 programmes	x	x	-	5.7%	6.0%	5.2%	5.4%	4.7%	5.1%
	x	-	x	10.1%	11.1%	10.5%	12.0%	11.0%	12.7%
	-	x	x	6.8%	5.7%	6.3%	5.3%	5.6%	5.0%
1 programme	x	-	-	5.8%	6.6%	5.3%	5.6%	5.8%	6.1%
	-	x	-	2.1%	2.1%	1.5%	1.5%	1.2%	1.2%
	-	-	x	5.6%	5.1%	4.1%	3.7%	3.6%	3.2%
Non-participation	-	-	-	17.4%	15.8%	10.7%	10.2%	8.9%	8.4%

Appendix table 2 Concurrent participation stratified by SES

Participation	Breast	Cervix	Colorectal	Low		Under median		Median		Over median		High	
				55	60	55	60	55	60	55	60	55	60
3 programmes	x	x	x	38.5%	36.5%	42.0%	43.7%	55.5%	55.3%	57.9%	57.6%	50.4%	51.2%
2 programmes	x	x	-	7.4%	6.7%	5.5%	6.0%	5.2%	5.4%	5.3%	5.5%	4.9%	4.5%
	x	-	x	11.0%	10.8%	10.2%	11.5%	10.7%	12.0%	9.8%	11.7%	10.4%	12.2%
	-	x	x	6.1%	5.5%	6.6%	5.4%	6.0%	5.3%	6.8%	5.6%	8.5%	9.2%
1 programme	x	-	-	6.4%	8.3%	6.6%	7.1%	5.5%	5.9%	5.0%	5.5%	5.1%	5.1%
	-	x	-	1.5%	2.1%	2.3%	2.3%	1.5%	1.5%	1.5%	1.4%	1.5%	1.9%
	-	-	x	6.9%	8.7%	6.2%	5.5%	4.3%	3.8%	3.9%	3.6%	5.7%	4.8%
Non-participation	-	-	-	22.3%	21.3%	20.5%	18.5%	11.3%	10.7%	9.8%	9.2%	13.5%	11.0%

Appendix table 3 Concurrent participation stratified by timing of invitations at age 55

Participation	Breast	Cervix	Colorectal	<3 months	3-6 months	>6 months
3 programmes	x	x	x	53.2%	53.2%	54.0%
2 programmes	x	x	-	5.0%	5.3%	6.4%
	x	-	x	10.9%	10.7%	10.2%
	-	x	x	6.0%	6.2%	5.3%
1 programme	x	-	-	5.3%	5.6%	5.7%
	-	x	-	1.5%	1.7%	1.6%
	-	-	x	4.6%	4.5%	4.5%
Non-participation	-	-	-	13.4%	12.9%	12.2%



4

Cumulative risks of false positive recall and screen-detected breast cancer after multiple screening examinations

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ABSTRACT

Women tend to make a decision about participation in breast cancer screening and adhere to this for future invitations. Therefore, this study aimed to provide high-quality information on cumulative risks of false-positive (FP) recall and screen-detected breast cancer over multiple screening examinations. Individual Dutch screening registry data (2005-2018) were gathered on subsequent screening examinations of 92,902 women age 49-51y in 2005. Survival analyses were used to calculate cumulative risks of a FP and a true-positive (TP) result after seven examinations. Data from 66,472 women age 58-59y were used to extrapolate to eleven examinations. Participation, detection, and additional FP rates were calculated for women who previously received FP results compared to women with true negative (TN) results. After seven examinations, the cumulative risk of a TP result was 3.7% and the cumulative risk of a FP result was 9.1%. After eleven examinations, this increased to 7.1% and 13.5%, respectively. Following a FP result, participation was lower (71-81%) than following a TN result (>90%). In women with a FP result, more TP results (factor 1.59 (95%CI:1.44-1.72)), more interval cancers (factor 1.66 (95%CI:1.41-1.91), and more FP results (factor 1.96 (95%CI:1.87-2.05)) were found than in women with TN results. In conclusion, due to a low recall rate in the Netherlands, the cumulative risk of a FP recall is relatively low, while the cumulative risk of a TP result is comparable. Breast cancer diagnoses and FP results were more common in women with FP results than in women with TN results, while participation was lower.

INTRODUCTION

Population-based breast cancer screening programmes have been shown to reduce breast cancer mortality by detecting breast cancers earlier.[1] Because of this, many Western countries have implemented a national or regional breast cancer screening programme for their citizens.[2] Within these programmes, women between age 50 and 69, but sometimes also slightly younger or older, are invited for breast cancer screening annually, biennially, or triennially.[2] This means that these women are invited to participate in multiple breast cancer screening examinations during their life.

In addition to the reduction in breast cancer mortality, the detection of earlier stage cancers also leads to less invasive treatment, potentially leading to an increase in quality of life.[3] However, breast cancer screening is also associated with harms including overdiagnosis and false positive (FP) screening results.[4, 5] Many studies investigated the extent of these harms to be able to weight them against the benefits, but also to be able to inform the invited women so they can make an informed decision whether to participate or not. In these studies the extent of overdiagnoses and FP results of a screening programme were found to differ substantially between countries.[6, 7] These differences in FP rate can mainly be attributed to differing aspects of the screening programmes, such as programme organisation (i.e. extent of centralisation, single versus double reading, experience of radiologists, screening interval, and age of the population invited) and cultural factors (i.e. risk aversion and litigation culture).[6, 7] For example, the specificity of subsequent breast cancer screening examinations in Denmark is considerably higher than that in the United States (US) (99% compared to 92%), and Denmark, thus, has a substantially lower FP rate.[7]

In the Netherlands, women are invited for breast cancer screening with digital mammography biennially between the ages of 50 and 74. The programme has a relatively low recall rate of 2.4% which leads to a FP rate of 1.7%.[8] This percentage also represents the average risk of a screening test resulting in a FP result. However, since women are invited up to thirteen times in their lives, it is important to provide high-quality information on the cumulative risks over multiple screening examinations to enable women to make an informed decision about participating. Re-attendance is high in the Netherlands and it is suggested that most women make a decision about participation and adhere to this decision for future invitations.[8, 9] Therefore, presenting risks over multiple screening examinations is crucial to enable women to make an informed choice. Furthermore, the rate of FP results per true positive (TP) result gives an indication of the balance between short-term screening benefits and harms in a specific screening programme. It is known that this rate is higher in the initial screening examination than in subsequent examinations.[8, 10] However, it is uncertain what this rate will be over multiple examinations cumulatively.

Several studies have analysed cumulative risks of FP results over multiple screening examinations in different countries and found ranges from 8% to 61% over ten examinations for women with an average breast cancer risk.[11-16] The biggest difference was seen when comparing results from studies in the United States to those in Europe, due to the difference in screening interval and recall rate. Within Europe, where screening intervals and recall rates are more comparable, only a few countries calculated cumulative risks. Despite this comparability in programme, the cumulative risks still ranged between 8% and 23% over ten screening examinations.[11-14] Specifically for the Dutch breast cancer screening programme, analyses were performed for thirteen examinations which resulted in a cumulative risk of FP results ranging of 16.1%.[17] In this study, data from women starting screening in 1975-1976 were used and data on five screening examinations from women starting screening in 1997 were extrapolated using the data from 1975 and incorporating the expected effect of digital mammography. However, in the meantime, changes have been made in the programme such as the introduction of digital mammography, the implementation of two-view mammography in both initial and subsequent screening examinations, and changes to the referral strategy including the use of the Breast Imaging-Reporting and Data System (BI-RADS) categories which affected the amount of FP results.[3, 18, 19]

Furthermore, international studies found that women who previously had a FP result are more likely to be diagnosed with breast cancer later on.[20-23] The reported hazard rates (HRs) and relative risks (RRs) were between 1.67 and 2.18 for women who previously had a FP result and increased to HRs between 4.22 and 9.13 for women who had multiple FP results.[20-23] Risks of both screen-detected and interval cancers were found to be increased and remained higher until twelve years after receiving the FP result.[23] This suggests that there might be some underlying biological susceptibility that causes some of the excess cancer risk in women with a FP test.[20] However, since FP rates differ between countries, it can be expected that the population of women with a history of a FP result and their risk factors are different as well. Therefore, it is unclear if, and to what extent FP results in the Dutch breast cancer screening programme lead to an increased risk of a breast cancer diagnosis. This is especially relevant since women were found to be less likely to participate in screening after a FP result in the Dutch breast cancer screening programme.[24]

Therefore, this study aimed to estimate the cumulative risk of false positive recall and screen-detected breast cancer after multiple screening examinations in the Netherlands using more recent data. Furthermore, this study aimed to investigate screening behaviour and outcomes in women with a history of FP results.

METHODS

The population-wide breast cancer screening programme in the Netherlands started in 1990 with biennial mammography screening for women aged 50 to 69. In 1998, this age-range was extended to also include women aged 70 to 74. Initially, screen-film mammography was used, but this was gradually replaced for full-field digital mammography between 2003 and 2010. Mammographic examinations were performed by specialised radiographers who checked the images and immediately repeat examinations in case of vagueness or incompleteness. Independent double reading is performed by specialised screening radiologists who use the BI-RADS system to classify mammograms. In the Netherlands, women with a BI-RADS score of 0, 4, and 5 are referred for follow-up testing.[18] BI-RADS 3 is not used.

Data collection

Data were retrieved from the Netherlands cancer registry (NKR) at the Netherlands Comprehensive Cancer Organisation (IKNL). The dataset included data on screening invitations, participation, and outcomes. Furthermore, the age of the women at each screening examination was included. Participation was defined as a screening test registered after a screening invitation and before the sending of the invitation of the subsequent examination (i.e. approximately 24 months).

At the start of the screening programme, screening data were stored in multiple regional screening registries. More recently, the data was brought together in a national database. However, due to differences in registries, data from before 2005 were incomplete which made the data unreliable for this analysis. Therefore, we chose to only include data from screening invitations sent from the year 2005 onwards.

During the time period 2005-2019, women who regularly received biennial breast cancer screening invitations could have been invited for breast cancer screening seven or eight times. Women who moved to another municipality in the meantime could have received more or less invitations and women who permanently unregistered for breast cancer screening or had breast cancer received less invitations.

Population

This longitudinal, observational cohort study included two cohorts of women who were invited for breast cancer screening. The first cohort included women invited for the first time in 2005; first-time invitees. These women were either 49, 50, or 51 years of age in 2005. The second cohort included women who were 58 or 59 years of age in 2005, thus, in 2005 they were invited for breast cancer screening for the fifth or sixth time in their life.

Women who did not participate after the screening invitation in 2005 were excluded from analysis. Both cohorts were followed over multiple screening examinations ending with invitations sent until December 31st in 2018. Participation and result data were included until early 2020.

Statistical analyses

Because data were only available from 2005 onwards, the analyses included seven consecutive screening examinations of the thirteen that were offered in the Dutch breast cancer screening programme. However, by using the data of a second cohort of older women, extrapolation was possible until eleven examinations of screening (Figure 1).

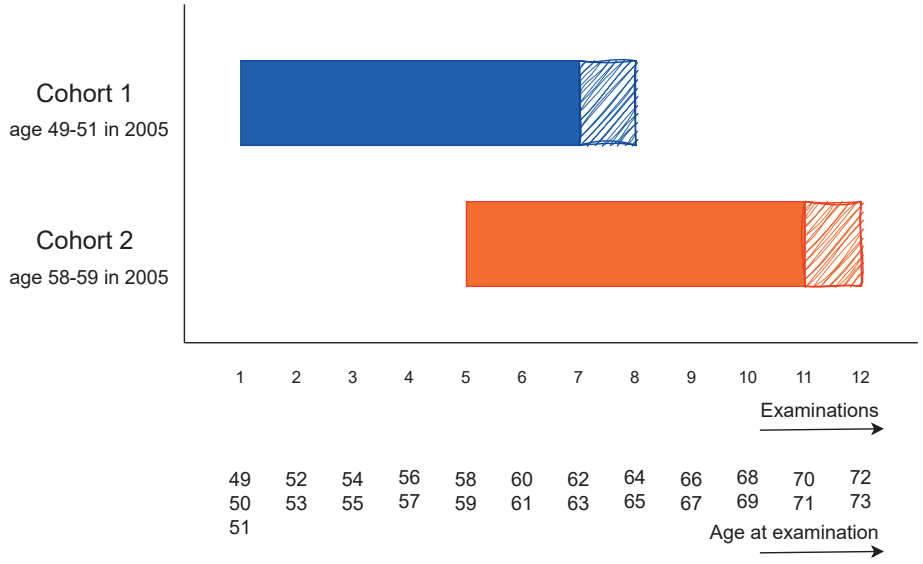

Figure 1 construction of cohorts

Life table survival analyses were performed with data from the cohort of first-time invitees to evaluate the cumulative risk of receiving 1) a FP or 2) a TP screening result (i.e. breast cancer diagnosis) for the first seven screening examinations. Follow-up time was censored if a woman had a TP or FP result (only first FP results were analysed), if a woman stopped participating in screening (lost-to-follow up), or when the end of the data collection was reached. Of the women who were still in the analysis after seven screening examinations, we assumed 91% of the participants to also participate for the 8th examination and therefore have a longer follow-up time.[8] Cumulative risk of having received a FP or TP result were calculated per each consecutive examination to a maximum of seven examinations of participation and presented in percentages with accompanying 95% confidence intervals (95% CI).

A similar survival analysis was performed for the second cohort of women. Assuming equal risks between the first cohort and second cohort at equal ages, the results from the survival analysis of the second cohort were used to extrapolate the cumulative risk for additional examinations. The increase in cumulative risk per examination in cohort two was applied to the cumulative risk after seven examinations in the first cohort. This allowed for extrapolation of cumulative risks up until eleven screening examinations.

Furthermore, among the first-time invitees cohort, participation in screening examinations subsequent to a true negative (TN) result was compared to participation subsequent to a FP result. In addition, the rates of breast cancer diagnoses and additional FP results were compared between women who previously received TN results and women who had a history of FP results per 1000 screens. Statistical analyses were performed in IBM SPSS Statistics version 28.

RESULTS

In total, data were received from 115,122 women who received their first invitation for breast cancer screening in 2005 (cohort 1). Among them, 92,902 (80.7%) participated in this first screening examination. The second cohort consisted of 66,472 women who participated in the screening examination in 2005. After the screening examination in 2005, 97.1% of the first-time invitees and 98.7% of the older women received a TN screening result (Table 1). Furthermore, the TP rate was 5.0 and 4.3 per 1000, and the FP rate was 21.5 and 6.5 per 1000, respectively. This resulted in 4.3 FP results per TP in the first screening examinations in 2005 and 1.5 FP results per TP in the fifth or sixth examination in 2005. In both cohorts, the interval cancer (false negative (FN) screen) rate was 2.4 per 1000.

Table 1 population characteristics

	Cohort 1	**Cohort 2**
	First-time invitees in 2005	**5th or 6th invitation in 2005**
Age range	49-51	58-59
n	92,902	66,472
Average number of invitations received between 2005 and 2019	6.9 (sd 1.1) (range 1-10)	6.8 (sd 1.1) (range 1-12)
Times participated	6.2 (sd 1.7) (range 1-9)	6.3 (sd 1.5) (range 1-9)
Result screening examination in 2005		
TP	464 (5.0 per 1000)	288 (4.3 per 1000)
FP	1998 (21.5 per 1000)	435 (6.5 per 1000)
TN	90,213 (971.1 per 1000)	65,588 (986.7 per 1000)
Interval cancer (FN)	227 (2.4 per 1000)	161 (2.4 per 1000)
FP/TP ratio	4.3	1.5

* standard deviation (sd)

Survival analyses found that after seven screening examinations the cumulative risk of at least one FP result was 9.1% (95%CI: 8.9%-9.4%) and of a TP result was 3.7% (95%CI: 3.6%-3.9%) (Appendix Table 1). The extrapolated cumulative risks show an increase in cumulative risk to 13.5% (95%CI: 13.1-13.9) for FP results and 7.1% (95%CI: 6.8-7.5) for TP results after eleven screening examinations. The FP/TP ratio was highest after one or two examinations (3.8) and decreased after an increasing number of examination and an increase in age of the women (2.5 after seven examinations and 1.9 after eleven). During the first examination the highest percentage of FP results was found, after which the increase in cumulative risk seemed to follow a less steep linear trend (Figure 2). After a relative high number of TP results during the first examination, the cumulative risk increased more slowly followed by an increasing steepness during later examinations at higher age.

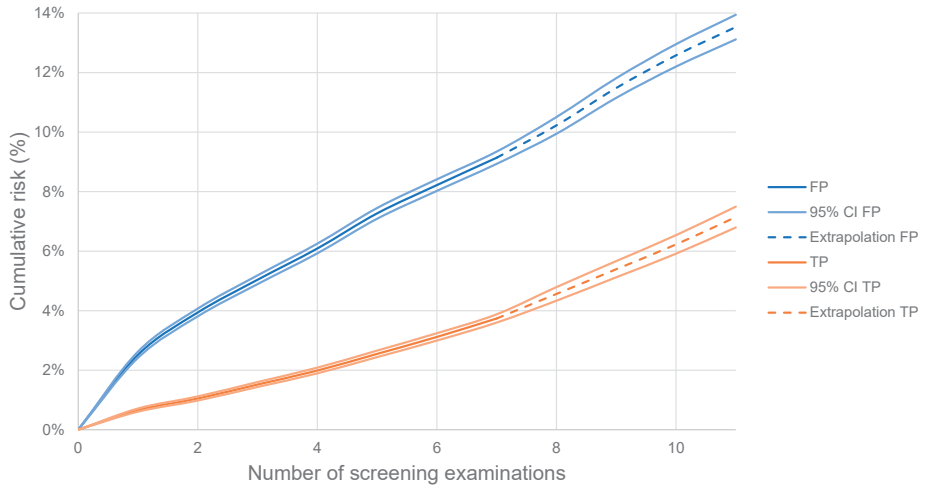

Figure 2 Cumulative risk of FP and TP screening results over 11 screening examinations. The dashed lines represent the extrapolation of results based on data from cohort 2.

Participation in the screening examination following a TN screening result was found to be over 90%, independent of the examination in which the TN result was received (Figure 3). When a FP result was received in the first screening examination, participation in the second examination was 71%. However, the later the FP result was received, the higher the participation rate in the subsequent examination with a maximum of 81% participation in examinations 6 and 7. Even though the participation rate increased as the FP was received later, it was always lower than when a TN result was received.

In the screening examinations following a TN result, 34.6 per 1000 screens performed resulted in a FP result, 16.5 per 1000 in a TP result, and 5.0 per 1000 in a FN result (Table 2). Resulting in a total of 21.5 breast cancer diagnosis per 1000 screens performed. Among

women who previously had a FP result, per 1000 screens 67.8 were FP, 26.1 were TP, and 8.2 were FN. Compared to women with TN results, women with a FP result had 1.96 times as many FP results (95% confidence interval (CI) 1.87-2.05), 1.59 times as many TP results (95%CI 1.44-1.72), and 1.66 times as many FN results (95%CI 1.41-1.91). Combining TP and FN results in total number of breast cancer diagnoses, women with a previous FP result had 1.60 times as many diagnoses per 1000 screens (95%CI 1.48-1.72).

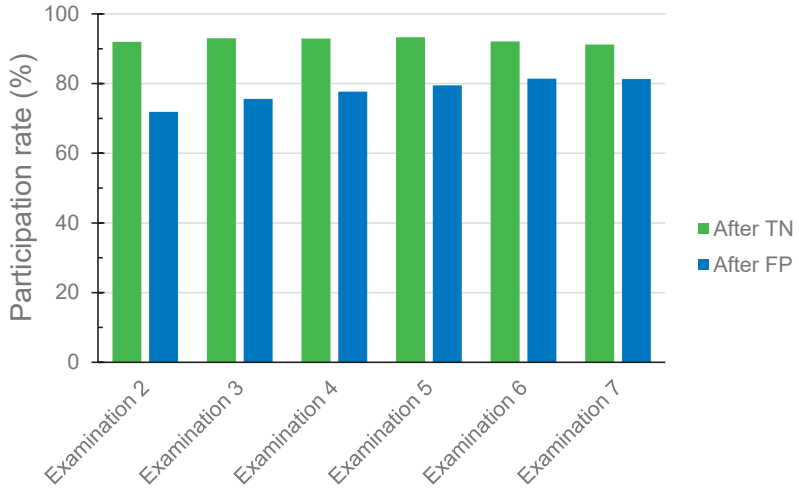

Figure 3 Participation in breast cancer screening stratified by previous screening result.

Table 2 FP, TP, FN, and BC results in screening examinations following TN and FP results

	After TN (516,918 screens)				**After FP** (7,406 screens)			
	FP	**TP**	**FN**	**BC** (TP+FN)	**FP**	**TP**	**FN**	**BC** (TP+FN)
Examination 2	1,062	270	217	487	34	4	6	10
Examination 3	1,705	677	374	1,051	75	15	8	23
Examination 4	2,598	1,100	431	1,531	94	41	11	52
Examination 5	3,948	1,724	655	2,379	85	48	16	64
Examination 6	4,037	2,284	633	2,917	100	40	13	53
Examination 7	4,521	2,474	254	2,728	114	45	7	52
total	17,871	8,529	2,564	11,093	502	193	61	254
/1000	34.6	16.5	5	21.5	67.8	26.1	8.2	34.3
95% CI	*34.1-35.1*	*16.2-16.8*	*4.8-5.2*	*21.1-21.9*	*62.1-73.5*	*22.4-29.7*	*6.2-10.3*	*30.2-38.4*
Rate FP/ rate TN					1.96	1.59	1.66	1.6
95% CI					*1.87-2.05*	*1.44-1.72*	*1.41-1.91*	*1.48-1.72*

* 95% confidence interval (95% CI)

DISCUSSION

This study found that women who participated in the first seven screening examinations of the Dutch breast cancer screening program had a cumulative risk of 3.7% to have a screen-detected breast cancer and a 9.1% cumulative risk of having a FP screening result. This was expected to increase to 7.1% and 13.5%, respectively, after eleven screening examinations. In women who previously had a FP result, we found that the participation rate was lower than in women who had TN results. The difference between these two groups was most pronounced when women received a FP result in the first screening examination. In addition, women with a history of FP results had nearly twice as many additional FP results, and a 60% increase in breast cancer diagnoses compared to women with TN screening results. This increase in breast cancer diagnoses was observed in both screen-detected and interval cancers.

A study in Finland found a cumulative risk of a screen-detected breast cancer of 3.4% over seven screening examinations and 5.7% over ten examinations with the highest risk in women with a history of breast cancer symptoms.[11] Furthermore, a Spanish study found that women with a history of benign breast disease had a cumulative risk of 3.6%, women with a family history of breast cancer had a cumulative risk of 4.5%, women with both had a risk of 6.1% and women with neither had a cumulative risk of 2.6% over seven screening examinations.[25] The weighted average of these four groups would come down to a cumulative risk of 3.0%. Compared to our results on TPs, the Finnish and Spanish risks are a little lower. A reason for this is the lower breast cancer incidence in both countries compared to the Netherlands.[26] However, also differences in screening detection performance may play a role.[27] A previous study on the Dutch breast cancer screening programme predicted that the cumulative risk of a screen-detected breast cancer after implementation of digital mammography would be 7.1% over thirteen examinations of screening.[17] Our study already found a cumulative risk of 7.1% after eleven examinations. The increase in cumulative risk can probably be explained by the usage of data from a more recent cohort of women who have a higher risk of developing breast cancer.[28]

Only a few studies present the cumulative risk of a FP result after seven examinations of breast cancer screening. A study in Spain found cumulative risks between 20.7% and 34.3% depending on family history and previous benign breast disease, an Italian study found a cumulative risk of 15.2%, and a Finnish study found a cumulative risk of 13.6% to receive a FP result after seven examinations.[11, 25, 29] All three estimates are higher than the cumulative risk of 9.1% that we found after seven examinations in the current study. More European studies reported cumulative risks after ten screening examinations and found estimates between 8% and 23%.[11-14] Only the cumulative risk of 8% found in the region of Fyn in the

Danish study was lower than the 12.6% the current study found after ten examinations of screening.[14] The estimate for the Copenhagen region and the other studies were all higher than the 12.6% we found over ten examinations and also higher than the 13.5% we found for eleven screening examinations. In addition, two American studies found even higher cumulative risks between 38.1% and 42% after five examinations of biennial screening and between 56.3% and 61.3% after ten examinations of annual screening.[15, 16] The considerable difference between most European countries and the US can probably be explained because of the lower recall rate in most European countries compared to the US.[7] Even within Europe, recall rates differ and can explain the differences between countries, but also differences in calendar year of data used could have an influence.[27] Additionally, the study by Ho et al. found that screening with digital breast tomosynthesis (DBT) instead of digital mammography can decrease the cumulative risk of a FP results by 6.7% point in annual and 2.4% point in biennial screening.[16] In the US DBT is used in a proportion of the screening settings, while in Europe DBT is hardly used in screening, which can also explain part of the difference between the estimates in the US and Europe.

Overall, the cumulative risks on FP and TP results in the Netherlands are relatively favourable compared to other countries. Despite the lower recall rate in the Netherlands, the cumulative risk of a screen-detected breast cancer is still quite comparable. This is an indication that the lower recall rate did not compromise the detection rate. This was also reflected in the low FP/TP ratios found, compared to a FP/TP ratio of 3.2 after ten examinations in Finland and of the pooled estimate of 2.8 presented in the 'balance sheet' by Paci et al. based on European data and studies.[11, 30] Especially considering the usage of digital mammography in the majority of screens performed in the current study which was usually found to yield a higher FP rate.[31] In addition, it shows that the Dutch policy of not including follow-up diagnostic assessment as part of the screening programme did not compromise the cumulative FP and TP rates. This low FP/TP ratio is expected to translate into a favourable ratio in long-term harms and benefits.

Previously reported HRs and RRs for breast cancer diagnosis after a FP result were between 1.7 and 2.2 for women who previously had a FP result and increased to 4.2-9.1 for women who had multiple FP results.[20-23] The increased incidence ratio in our study was 1.59 for screen-detected cancers and 1.66 for interval cancers which is in line with the lower rates found in the previous studies. However, some studies found that part of the FP results were misclassified because of a false negative diagnostic assessment (FNDA) which would be the case for 0.6% to 1.5% of recalled women.[20, 21] After exclusion of these women, the HR in Flanders decreased from 1.9 to 1.5 and the RR in Denmark decreased from 1.7 to 1.3.[20, 21] It is unclear whether FNDA occurs in the Netherlands, and if so, to what extent this

happens. Unfortunately, the data required to investigate this was unavailable. Therefore, it was not possible to adjust for this in the current analysis.

Participation among women with a TN result was found to be high, over 90%, which is in line with the participation loyalty in the monitors of the Dutch screening programme.[8] Among women with a TP result, participation was found to be lower. This was also found in two previous studies in the Netherlands which found even lower participation rates of around 65% among women with a FP result compared to 93-95% among women with a negative screening result.[9, 24] However, Setz-Pels et al. also found that nearly 30% of women with a FP result had follow-up surveillance in the hospital, which suggested that the mammography coverage, i.e. screening coverage and hospital surveillance combined, in women with a history of FP results would be almost as high as for women with a negative screening result.[9] On the other hand, a study in Copenhagen did not find any difference between women with a negative and women with a FP screening result in their participation rate in the next round.[32] Interestingly, Chiarelli et al. found that, in Ontario, re-attendance of previously FP women was lower in screening centres without an assessment programme, like the policy in the Netherlands, and equal to negative women in centres with an assessment programme, like the policy in Denmark.[33] Since screening centres in the Netherlands do not have assessment included, while in Denmark assessment is part of the screening programme, this might explain the difference in re-attendance behaviour.

A strength of this study was the use of registry data, which included practically all screening invitations and tests performed in the Netherlands. Unfortunately, data from before 2005 were incomplete, which restricted the data to only include seven screening examinations of the thirteen that were offered in the Dutch breast cancer screening programme. However, by using the data of the second cohort of older women, extrapolation was possible until eleven examinations of screening. This extrapolation was performed under the assumption that both cohorts were equal in breast cancer risk at the screening examination extrapolated. This assumption largely holds, because during those screening examinations, the women in both cohorts would have had the same age. This was confirmed by comparable increases in cumulative risk of FP and TP results between examinations 5 and 7, of which data were available for both cohorts. A difference in risk could have been caused by a difference in birth cohort risk as shown by van der Waal et al. and Napolitano et al., but this effect was expected to be relatively small since the age difference was only nine years.[28, 34] Even though the extrapolation is less precise than analysis based on observed data, the benefit of this was that the cumulative risks are more applicable to women eligible for screening in current times, because screening performance has changed due to the implementation of digital mammography and because the breast cancer risk has increased over the years.[28, 35]

Given that most women in the Netherlands seem to make a fundamental decision about participation in breast cancer screening and adhere to this decision for future invitations, it is important that this decision is based on information encompassing benefits and harms of participation in multiple screening examinations. In addition, providing stratified information on increased risks in women who previously had a FP outcome may give them insights into their personal risk of developing breast cancer and may potentially increase their participation to the screening programme. Furthermore, in the prospect of risk stratified screening, it may be useful to include history of FP results into consideration when forming risk groups.

To conclude, we found that women who participate in the Dutch breast cancer screening programme have a cumulative risk of 3.7% to receive a TP result and of 9.1% to receive a FP result after seven screening examinations. After eleven examinations, these risks would increase to 7.1% for a TP result and 13.5% for a FP result. Due to the low recall rate in the Netherlands, these cumulative risks are relatively favourable compared to screening programmes in other countries, which is also represented in a favourable FP/TP ratio which is expected to translate in a favourable ratio in long-term harms and benefits. Furthermore, women who previously received a FP result more often receive TP and FP results in later examinations and more often have interval cancers while their participation rate in subsequent examinations is lower compared to women with TN results.

Conflict of interest

Dr. van Ravesteyn reports receiving fees for consulting from Wickenstones (paid to institution). Prof. dr. de Koning declares receiving fees for lectures at symposia for TEVA, Menarini, and Astra Zeneca (less than €1,000 and for reviewing external model analyses for Bayer (less than €1,000). The other authors have no conflicts to declare.

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Author contributions

LK: Conceptualisation, methodology, formal analysis, investigation, writing – original draft, visualisation; NvR: Conceptualisation, methodology, validation, writing- review & editing, supervision, funding acquisition; SC: Conceptualisation, Methodology, validation, writing- review & editing; EH: Conceptualisation, validation, writing- review & editing; JO: Conceptualisation, validation, writing- review & editing; MB: Conceptualisation, validation, writing- review & editing, funding acquisition; HdK: Conceptualisation, writing- review & editing, supervision, funding acquisition. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Ethics statement

Ethical approval was not applicable. In the Netherlands, implicit informed consent to pseudonymised cancer screening data use in research is recorded when one takes up the offer of screening. All individuals were informed that they could explicitly withdraw consent.

Data availability statement

The data used in this study are from the Netherlands Cancer Registry (NCR) and property of the Netherlands Comprehensive Cancer Organisation (IKNL). Data from the NCR can be requested at IKNL via https://iknl.nl/en/ncr/apply-for-data. Further information is available from the corresponding author upon request.

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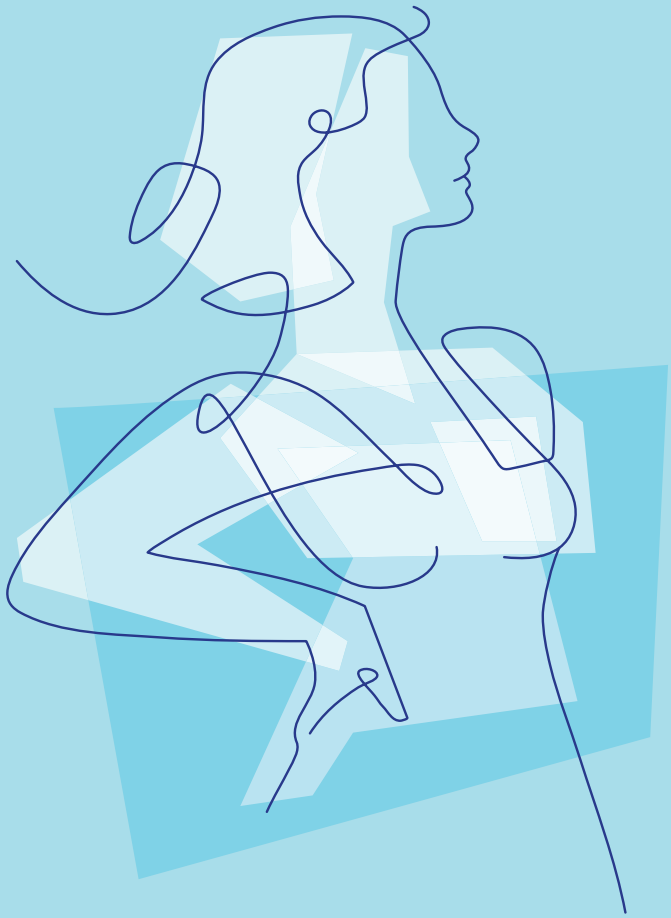
APPENDIX

Appendix Table 1 Cumulative risk of FP and TP results after one to eleven examinations of breast cancer screening

	Cumulative risk of a FP result	95% CI	Cumulative risk of a TP result	95% CI	FP/TP ratio
After 1 examination	2.5%	(2.4-2.6)	0.7%	(0.6-0.7)	3.8
After 2 examinations	3.9%	(3.8-4.1)	1.1%	(1.0-1.1)	3.8
After 3 examinations	5.0%	(4.9-5.2)	1.5%	(1.4-1.6)	3.3
After 4 examinations	6.1%	(5.9-6.3)	2.0%	(1.9-2.1)	3.1
After 5 examinations	7.3%	(7.1-7.5)	2.6%	(2.4-2.7)	2.9
After 6 examinations	8.2%	(8.0-8.4)	3.1%	(3.0-3.2)	2.6
After 7 examinations	9.1%	(8.9-9.4)	3.7%	(3.6-3.9)	2.4
After 8 examinations *	10.2%	(9.9-10.5)	4.6%	(4.3-4.8)	2.2
After 9 examinations *	11.5%	(11.2-11.8)	5.4%	(5.1-5.7)	2.1
After 10 examinations *	12.6%	(12.2-13.0)	6.2%	(5.9-6.5)	2.0
After 11 examinations *	13.5%	(13.1-13.9)	7.1%	(6.8-7.5)	1.9

* Results after 8-11 examinations were calculated via extrapolation based on data from cohort 2.



5

Effects of Cancer Screening Restart Strategies after COVID-19 Disruption

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ABSTRACT

Background

Many breast, cervical, and colorectal cancer screening programmes were disrupted due to the COVID-19 pandemic. This study aimed to estimate the effects of five restart strategies after the disruption on required screening capacity and cancer burden.

Methods

Microsimulation models simulated five restart strategies for breast, cervical, and colorectal cancer screening. The models estimated required screening capacity, cancer incidence, and cancer-specific mortality after a disruption of six months. The restart strategies varied in whether screens were caught up or not and if so, immediately or delayed, and whether the upper age limit was increased.

Results

The disruption in screening programmes without catch-up of missed screens led to an increase of 2.0, 0.3, and 2.5 cancer deaths per 100 000 individuals in ten years in breast, cervical, and colorectal cancer, respectively. Immediately catching-up missed screens minimised the impact of the disruption, but required a surge in screening capacity. Delaying screening, but still offering all screening rounds gave the best balance between required capacity, incidence, and mortality.

Conclusions

Strategies with the smallest loss in health effects were also the most burdensome for the screening organisations. Which strategy is preferred depends on the organisation and available capacity in a country.

BACKGROUND

Many European countries have adopted mass screening programmes for breast, cervical, and colorectal cancer. These screening programmes aim to detect pre-cancerous lesions and early stage cancers to allow for removal of lesions before progression to tumours and treatment of early stage cancers. Due to the early detection and treatment, screening programmes for breast, cervical, and colorectal cancer reduce cancer-specific mortality.[1-3]

The COVID-19 pandemic has affected cancer screening and treatment activities worldwide. In many countries, cancer screening programmes were paused since March 2020 causing a screening disruption for an unknown period of time.[4] Data from the nationwide Netherlands Cancer Registry showed that the number of breast, gynaecological, and gastrointestinal cancer diagnoses decreased steeply right after the start of the screening disruption.[5] It is likely that the disruption of screening activities explains, at least partly, this decrease in cancer diagnoses. In addition, many cancer treatments were delayed, because of the increased infection risk in hospitals and a reduced hospital capacity for non-COVID patients.[6] Prior studies have shown that a six month delay between a positive screening test and diagnostic testing led to reductions in prevented cervical and colorectal cancers and a less favourable stage distribution for breast and colorectal cancer.[7] An Australian modelling study estimated that a screening and treatment delay of six months would lead to progression from stage I to stage II cancer in 5% of breast cancers and 3% of colorectal cancers (detected and undetected).[8] These findings suggest that after the screening disruption more diagnoses will be classified as later stage cancer. The delay in screening and treatment of breast and colorectal cancer due to the COVID-19 pandemic was estimated to lead to an increase in cancer-specific deaths of 1% over a period of ten years in the USA.[9] However, it can be expected that the organisation of cancer screening highly influences the effect size of a screening disruption. Therefore, it is unknown what the effects of the screening disruption are on cancer incidence and cancer-specific mortality in Europe.

Besides screening organisation, the effects of the screening disruption are expected to be influenced by the length of the disruption and the way screening programmes are restarted after the disruption. Different restart strategies vary in whether screens are delayed or can be caught up, how fast this catch-up will be, whether screens are omitted because of the upper age limit, and which individuals are affected. This information is important for policy makers to decide which restart strategy to implement. Next to effects on incidence and mortality, policy makers are also interested in the screening capacity required per restart strategy to decide whether implementation is possible. At the moment, not much is known about the effects of restart strategies after a screening disruption. Therefore, the

aim of this study is to estimate the effects of different restart strategies for breast, cervical, and colorectal screening after the COVID-19 disruption, using microsimulation models.

METHODS

In this study, the effects of a six month disruption and different restart strategies were estimated using three MIcrosimulation SCreening ANalysis (MISCAN) models, specified for breast, cervical, and colorectal cancer screening (MISCAN-Breast[10], MISCAN-Cervix[11], MISCAN-Colon[12,13]). The three MISCAN models were developed by the Erasmus MC and simulate individual life histories of a population and, in a subset, the natural history of breast, cervical, or colorectal cancer, respectively. In addition, screening programmes can be simulated to estimate the effects of screening protocols on required screening capacity, cancer incidence and cancer-specific mortality. In this study, the models simulated the screening activities using Dutch population and screening data. The models MISCAN-Breast[10], MISCAN-Cervix[11], and MISCAN-Colon[12,13] are described in detail elsewhere.

Dutch national screening programmes

The Dutch breast cancer screening programme entails biennial digital mammography in screening centres and mobile units for women aged 50 to 75.[14] Because screening mainly takes place in mobile units, appointments are planned based on postal code. Therefore, the actual age at which a woman is screened differs per individual and is somewhere between the exact screening age and the two years after that. The mammograms are scored independently by two radiologists according to the Breast Imaging Reporting and Data System (BIRADS) classification. If the two radiologists report different BIRADS classifications, a third radiologist scores the mammogram. Women with BIRADS scores 4, 5 or 0 are referred to an outpatient clinic for additional imaging and possibly a biopsy.

The Dutch cervical cancer screening programme entails cervical swabs at the general practitioner (GP) in women aged 30, 35, 40, 50, and 60.[15] First, the swabs are tested for high-risk Human Papillomavirus (hrHPV). In case of a positive hrHPV test, the same swab is tested on cytology. Women can also request a self-sampling-test on which hrHPV can be tested. In case of a positive self-sampling-test, women are advised to go to the GP for a swab that can be tested on cytology. Women with a normal cytology result receive a repeat cytology test after six months, whereas women with an abnormal result are directly referred for colposcopy. Women who test hrHPV positive at age 40, 50, or 60 are invited again at age 45, 55, or 65. Also non-attenders at age 40 or 50 are invited for screening at age 45 or 55.

The Dutch colorectal cancer screening programme entails biennial faecal-immunochemical test (FIT) for men and women aged 55 to 75.[16] Individuals testing with a concentration exceeding the cut-off of 47 µg Haemoglobin (Hb)/g faeces are referred for diagnostic colonoscopy. Participants with a negative colonoscopy or colonoscopy with a single small distal tubular adenoma are re-invited in the programme after ten years.

Disruption and restart strategies

This study estimated the effects of five restart strategies after a disruption of six months (Table 1). In the first strategy (no catch-up), the screening activity during the disruption period was cancelled and not caught-up on. The screening activity after the disruption continued as planned. In the second strategy (everyone delay), all screening activity was postponed by the length of the disruption and continued in the order it was planned for the entire population until the stopping age. In breast cancer, this means that the last screen (between age 74 and 75.9) was omitted for only a fourth of the individuals (i.e. the women who were planned to be screened between age 75.5 and 75.9 would be delayed till after the stopping age). In cervical cancer, this means that the additional screen at age 65 (for women who tested hrHPV positive at age 60) was omitted. In colorectal cancer, this means that all screens at age 75 were omitted for everyone. In the 'everyone delay' strategy, the increased interval was not caught up on. The third strategy (first rounds no delay) was similar to the 'everyone delay' strategy; however, screening was not delayed for individuals who reach the first screening age after 2020. The fourth strategy (continue after stopping age) was similar to the 'everyone delay' strategy; however, the stopping age of the screening protocol was increased by the length of the disruption to ensure the same number of lifetime screening invitations as would have been the case without the disruption. In the last strategy (catch-up after stop), the disrupted screening activity was delayed for the length of the disruption. The screening activity planned after the disruption was not affected. Therefore, catch-up takes place at the same time as regular screening activity. The group of individuals who had one increased screening interval due to the disruption, had a decreased interval for the screening round following the delayed round (i.e. an interval of 2.5 years followed by an interval of 1.5 years for breast and colorectal cancer screening and an interval of 5.5 years followed by an interval of 4.5 years for cervical cancer screening). In addition, the stopping age was increased by the duration of the disruption for the individuals who were due for their last screening appointment at the time of the disruption. This was done to ensure that these individuals receive the same number of lifetime screening invitations as would have been the case without the disruption.

Table 1 Characteristics of investigated restart strategies

Restart strategy	Population affected	Duration of effects	Changes in stopping age
No catch-up	Population due for a screening appointment during the disruption	Only effects during the disruption	No changes in stopping age were needed
Everyone delay	Total population	The delay will exist forever	Individuals exceeding the original stopping age due to the delay missed their last invitation
First rounds no delay	Total population except individuals who reach the first screening age after 2020	All individuals eligible for screening in or before 2020 are delayed for all screening rounds	Individuals exceeding the original stopping age due to the delay missed their last invitation
Continue after stopping age	Total population	The delay will exist forever	The stopping age increased with the duration of the disruption
Catch-up after stop	Population due for a screening appointment during the disruption	The delay is caught up in the second half of 2020.	The stopping age increased with the duration of the disruption for the individuals who were invited for their last round in 2020

Model parameters

In this study, the models simulated a population of 500 million individuals to allow for robust estimates of differences between scenarios. The individuals were at average risk of cancer diagnosis and population characteristics were based on data from Statistics Netherlands[17] (i.e. birth and life tables) and the Netherlands Comprehensive Cancer Organisation[18] (cancer incidence and mortality). The screening disruption was modelled for the first six months of 2020. The assumption was made that the disruption in screening activity did not influence screening attendance after the disruption. Also, it was assumed that screening capacity was restored to at least 100% directly after the screening disruption.

Outcomes

Required screening capacity, cancer incidence, and cancer-specific mortality data from the models were transposed to rates per 100 000 individuals (per 100 000 women for breast and cervical cancer) in the total population. Screening capacity was split up into two outcome variables: rate of primary screening tests performed per year compared to undisrupted screening, and rate of follow-up tests compared to undisrupted screening. In breast cancer screening, follow-up testing was defined as the number of referrals after a primary screen, in cervical cancer screening this was defined as the number of colposcopies performed, and in colorectal cancer screening this was defined as the number of colonoscopies performed. Long-term cancer incidence and cancer-specific mortality rates were compared to model predicted cancer-specific incidence and mortality rates in a situation with undisrupted screening.

Sensitivity analyses

Sensitivity analyses were performed to estimate the effects of a disruption of 3, 9, or 12 months for all investigated restart strategies. For the 'catch-up after stop' strategy, the catch-up period was assumed to have the same length as the disruption period.

RESULTS

Required screening capacity

In the period 2020-2030, the required primary screening capacity for a situation with undisrupted screening was estimated to decrease for breast cancer (11 744 to 11 080 per 100 000), drop in 2022 for cervical cancer (5 439 to 4 116 per 100 000) and subsequently increase (4 401 per 100 000), and increase for colorectal cancer (10 128 to 11 317 per 100 000) (table 2). The required follow-up test capacity followed similar patterns (table 3).

For all cancer sites, the 'catch-up after stop' strategy required a yearly primary screen capacity equal to a situation with undisrupted screening. However, in 2020, all screening activity took place in the second half of the year. Therefore, the required capacity during the second half of 2020 was actually doubled in the 'catch-up after stop' strategy. The strategies 'no catch-up', 'everyone delay', 'first rounds no delay', and 'continue after stopping age' required a reduced capacity in 2020, followed by an equal or slightly reduced capacity in the years after the disruption. In 2022, the year of the second round in the new Dutch cervical cancer screening programme, the 'everyone delay', 'first rounds no delay', and 'continue after stopping age' strategies required an additional capacity of 17-18% compared to undisrupted screening.

The effects of the restart strategies on the required follow-up test capacity were similar to the effects on the required primary screening test capacity. Moreover, the 'catch-up after stop' strategy will require an increased follow-up capacity compared to undisrupted screening in 2020 for breast cancer and colorectal cancer (8% and 1%, respectively) leading to a more than doubled required follow-up capacity, because all screening took place in the second half of 2020. For cervical cancer, the required follow-up capacity for the 'catch-up after stop' strategy was -13% in 2020, which comes down to a 75% increase in the second half of the year, when all screening took place. Next to that, the required cervical cancer follow-up capacity remained increased in 2021 (12%). Furthermore, the required follow-up capacity for breast cancer screening in the 'everyone delay', 'first rounds no delay', and 'continue after stopping age' strategies were increased in 2021 and 2022. Additionally, the 'no catch-up' strategy required an increased follow-up capacity in breast and colorectal cancer screening in the year of the next screening round for individuals who missed their screen due to the disruption.

Table 2 Rate of primary screening tests required per restart strategy after a six month disruption compared to undisrupted screening, per 100 000 individuals per year (in %)

	Breast cancer						Cervical cancer						Colorectal cancer					
	Undisrupted screening	No catch-up[a]	Everyone delay[b]	First rounds no delay[c]	Continue after stopping age[d]	Catch-up after stop[e]	Undisrupted screening	No catch-up[a]	Everyone delay[b]	First rounds no delay[c]	Continue after stopping age[d]	Catch-up after stop[e]	Undisrupted screening	No catch-up[a]	Everyone delay[b]	First rounds no delay[c]	Continue after stopping age[d]	Catch-up after stop[e]
2020*	11.744	-50%	-51%	-50%	-50%	0%	5.409	-50%	-50%	-44%	-50%	0%	10.128	-50%	-53%	-47%	-50%	0%
2021	11.895	0%	-2%	2%	-1%	0%	5.439	0%	0%	0%	0%	0%	10.632	0%	-8%	-8%	-3%	0%
2022	11.719	0%	-1%	-1%	0%	0%	4.116	0%	18%	17%	18%	0%	10.400	1%	-6%	0%	1%	0%
2023	11.733	0%	-2%	2%	-1%	0%	4.100	0%	1%	0%	1%	0%	10.739	0%	-8%	-8%	-2%	0%
2024	11.601	0%	-1%	-2%	0%	1%	4.156	0%	0%	0%	0%	0%	10.656	1%	-6%	0%	0%	0%
2025	11.603	0%	-2%	2%	0%	0%	4.150	0%	-1%	8%	-1%	0%	10.974	0%	-7%	-7%	-2%	0%
2026	11.382	0%	-1%	-1%	0%	1%	4.184	0%	0%	0%	0%	0%	10.973	1%	-5%	0%	0%	0%
2027	11.410	0%	-2%	2%	-1%	0%	4.198	0%	0%	0%	0%	0%	11.122	0%	-6%	-7%	-1%	0%
2028	11.227	0%	-1%	-1%	0%	1%	4.261	0%	0%	0%	0%	0%	11.313	0%	-8%	-3%	-1%	0%
2029	11.225	0%	-2%	2%	-1%	0%	4.343	0%	-1%	-1%	-1%	0%	11.085	0%	-5%	-5%	1%	0%
2030	11.080	0%	-1%	-2%	0%	1%	4.401	0%	0%	9%	0%	0%	11.317	0%	-7%	-3%	-2%	0%

[a] The screening activity during the disruption period was cancelled and not caught-up on.

[b] All screening activity was postponed by the length of the disruption.

[c] All screening activity was postponed by the length of the disruption, but not for individuals who reached the first screening age after 2020.

[d] All screening activity was postponed by the length of the disruption and the stopping age is increased by the length of the disruption.

[e] The disrupted screening activity was caught-up immediately after the disruption at the same time as regular screening activity.

* Because of the disruption, all screens in 2020 were performed in the second half of the year. Therefore, a capacity change of -50% in 2020 represented a normal screening capacity during the second half of 2020 and a capacity change of 0% in 2020 represented a double capacity during the second half of 2020.

Table 3 Rate of follow-up tests required per restart strategy after a six month disruption compared to undisrupted screening, per 100 000 individuals per year (in %)

	Breast cancer						Cervical cancer						Colorectal cancer					
	Undisrupted screening	No catch-up[a]	Everyone delay[b]	First rounds no delay[c]	Continue after stopping age[d]	Catch-up after stop[e]	Undisrupted screening	No catch-up[a]	Everyone delay[b]	First rounds no delay[c]	Continue after stopping age[d]	Catch-up after stop[e]	Undisrupted screening	No catch-up[a]	Everyone delay[b]	First rounds no delay[c]	Continue after stopping age[d]	Catch-up after stop[e]
2020*	247	-50%	-45%	-44%	-44%	8%	196	-50%	-51%	-42%	-51%	-13%	447	-35%	-36%	-32%	-34%	1%
2021	251	0%	10%	13%	12%	0%	201	0%	-3%	1%	-3%	12%	465	0%	-4%	-4%	1%	0%
2022	248	19%	6%	6%	8%	-6%	163	0%	13%	14%	13%	0%	463	7%	-2%	1%	3%	-1%
2023	250	0%	1%	3%	2%	-1%	160	0%	-2%	-1%	-2%	0%	479	-5%	-10%	-9%	-5%	0%
2024	248	3%	0%	0%	2%	0%	162	0%	-3%	-1%	-3%	0%	484	2%	-3%	0%	2%	0%
2025	248	0%	0%	2%	2%	0%	164	0%	-5%	5%	-5%	-1%	495	-2%	-8%	-7%	-3%	0%
2026	245	1%	0%	-1%	2%	0%	166	0%	-4%	1%	-3%	0%	506	-1%	-4%	-2%	-1%	0%
2027	246	0%	-1%	2%	1%	0%	167	0%	-4%	-1%	-3%	0%	520	2%	-3%	-3%	1%	0%
2028	243	1%	0%	-1%	2%	1%	170	0%	-4%	-2%	-4%	0%	526	-1%	-6%	-4%	-1%	0%
2029	243	0%	-1%	2%	1%	0%	172	0%	-4%	-2%	-3%	0%	528	0%	-3%	-2%	1%	0%
2030	242	0%	0%	-1%	1%	1%	175	1%	-4%	5%	-3%	0%	538	-1%	-6%	-3%	-2%	0%

[a] The screening activity during the disruption period was cancelled and not caught-up on.

[b] All screening activity was postponed by the length of the disruption.

[c] All screening activity was postponed by the length of the disruption, but not for individuals who reached the first screening age after 2020.

[d] All screening activity was postponed by the length of the disruption and the stopping age is increased by the length of the disruption.

[e] The disrupted screening activity was caught-up immediately after the disruption at the same time as regular screening activity.

* Because of the disruption, all screens in 2020 were performed in the second half of the year. Therefore, a capacity change of -50% in 2020 represented a normal screening capacity during the second half of 2020 and a capacity change of 0% in 2020 represented a double capacity during the second half of 2020.

Cancer incidence

In breast and colorectal cancer, the 'catch-up after stop' strategy was estimated to lead to an increased incidence rate compared to undisrupted screening in 2020, followed by a small decrease in incidence in the year of the next screening appointment for the population which was disrupted (figure 1). On the contrary, the other four strategies were estimated to lead to an incidence drop in 2020, followed by an increased incidence for two years. This drop was larger for breast cancer (-29 per 100 000) than for colorectal cancer (-9 per 100 000). After 2025, all restart strategies had only minor deviations in incidence rate compared to undisrupted screening. For cervical cancer, all restart strategies resulted in similar patterns as for breast and colorectal cancer, though the effect size was much smaller and some increases in incidence occurred a year later.

Cancer-specific mortality

In figure 2, the cancer-specific mortality rates compared to undisrupted screening are shown as a moving average over three years per cancer site. The 'catch-up after stop' strategy resulted in a cancer-specific mortality rate similar to that for undisrupted screening between 2020 and 2060 in the three cancer sites. On the contrary, the 'everyone delay' strategy led to the largest increase in cancer-specific mortality rate over time (0.4 per 100 000 in breast cancer, 0.1 per 100 000 in cervical cancer, and 1.4 per 100 000 in colorectal cancer).

In the first years after disruption, the 'no catch-up', 'first rounds no delay', and 'continue after stopping age' strategies resulted in similar cancer-specific mortality rates as the 'everyone delay' strategy. After 2023, 2059, and 2040, the 'no catch-up' and 'first rounds no delay' strategies led to decreasing mortality rates for breast, cervical and colorectal cancer, respectively. For the 'no catch-up' strategy, the mortality rates returned to be equal to undisrupted screening after 2048, 2058, and 2056. For the 'first rounds no delay' strategy the mortality rates returned to be equal to undisrupted screening after 2050, 2085, and 2057. After 2023, 2031, and 2022, the 'continue after stopping age' strategy led to decreasing mortality rates for the three cancer sites, respectively. These mortality rates returned to be equal to undisrupted screening after 2047, 2040, and 2034.

The cumulative breast cancer and cervical cancer mortality rates over the ten years following the screening disruption (2020-2030) were the highest in the 'no catch-up' strategy (figure 3). The cumulative mortality rate was 2.0 per 100 000 for breast cancer (186 cases in the Dutch situation) and 0.3 per 100 000 for cervical cancer (27 cases in the Dutch situation). In colorectal cancer, the 'everyone delay' strategy led to the highest cumulative mortality rate (4.9 per 100 000; 740 cases in the Dutch situation). Smaller cumulative mortality rates were found for the other restart strategies, with the smallest rates for the

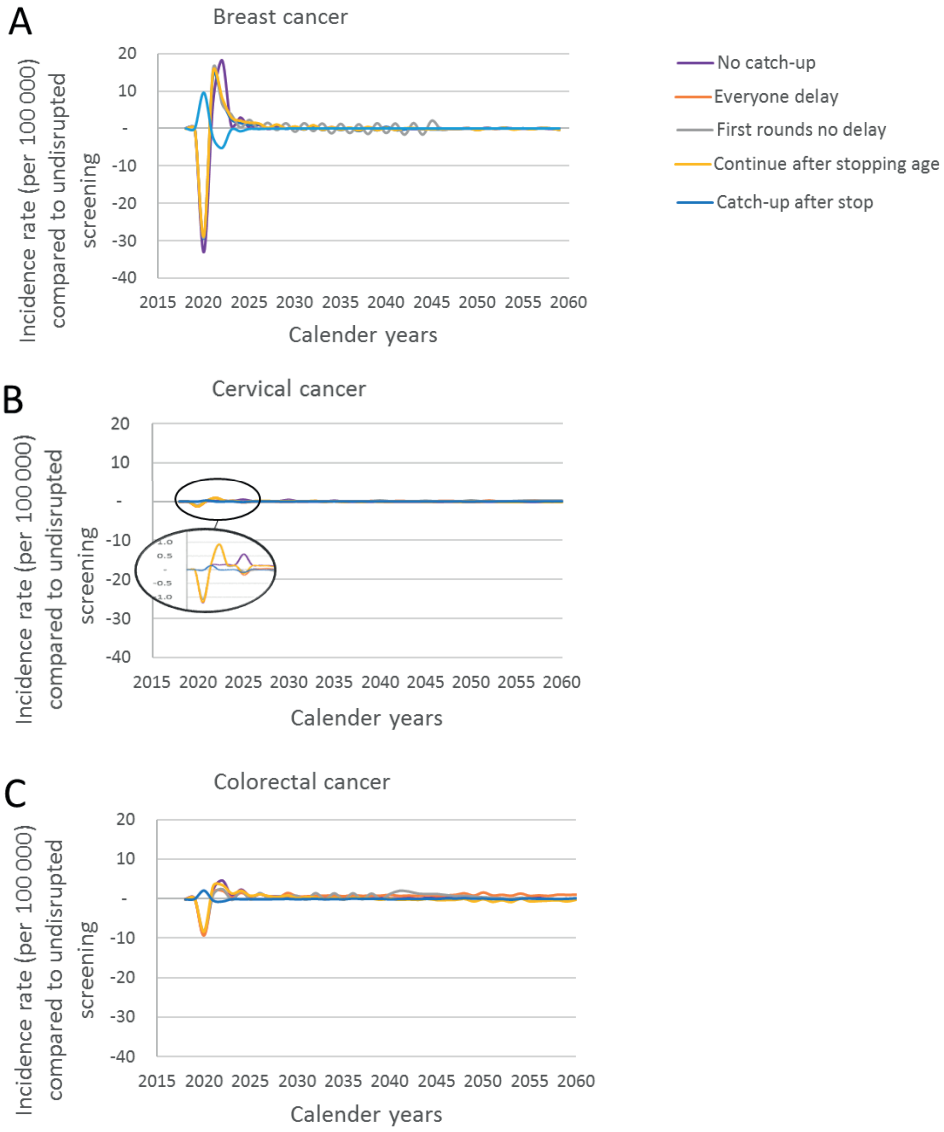

Figure 1 Cancer incidence rate (per 100 000) after a six month disruption compared to undisrupted screening over time for the different restart strategies. A) Breast cancer, B) Cervical cancer, C) Colorectal cancer

'catch-up after stop' strategy in all cancer sites. The absolute differences in cumulative cervical cancer mortality rates between the five restart strategies were small. In breast and cervical cancer, the 'no catch-up' strategy led to the highest mortality rates, whereas in colorectal cancer, the 'everyone delay' and 'first rounds no delay' strategies resulted in higher mortality rates.

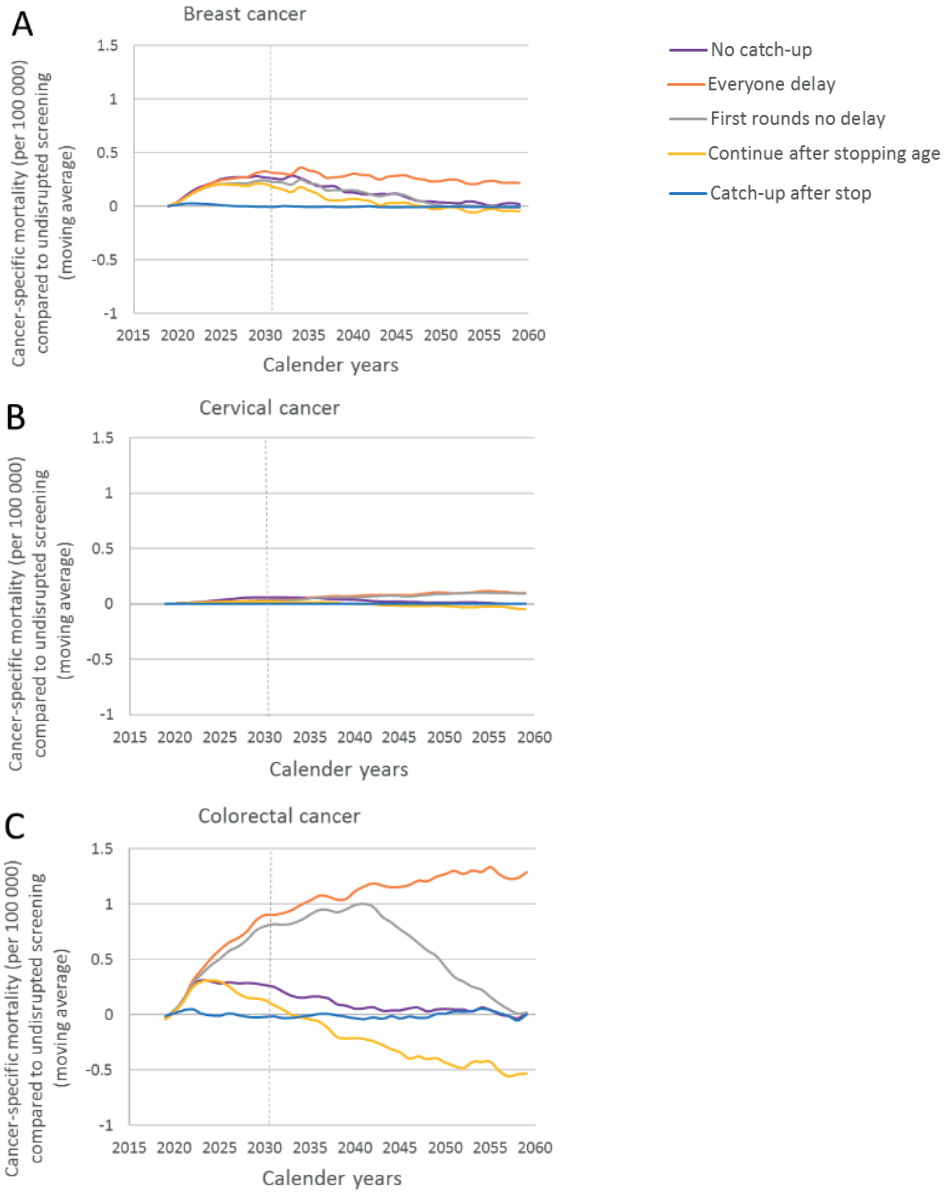

*Figure 2 Moving average of cancer-specific death rate (per 100 000) after a six month disruption compared to undisrupted screening over time for the different restart strategies. A) Breast cancer, B) Cervical cancer, C) Colorectal cancer. * The vertical dotted line represents the cut-off used in figure 3.*

Sensitivity analysis

In general, a delay of three months led to a lower cancer-specific mortality, while the nine and twelve month delays resulted in higher cancer-specific mortalities than for a six month delay (supplement figure 1). Relative differences between the restart strategies and cancer

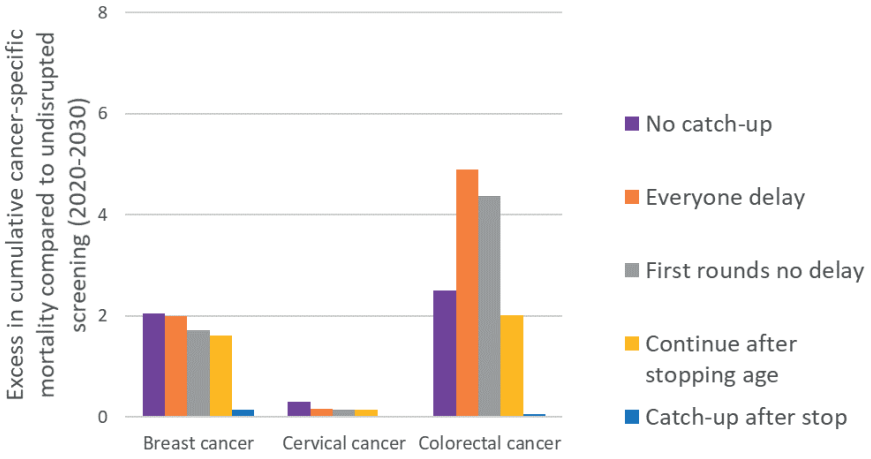

Figure 3 Cumulative excess in cancer-specific mortality rate (per 100 000) after a six month disruption compared to undisrupted screening over the years 2020-2030 for the different restart strategies

sites remained the same. The relative differences in mortality between disruptions of 3, 6, 9, or 12 months were the largest in breast cancer.

DISCUSSION

Using well-validated microsimulation models for three cancer sites, this study found that the impacts of a screening disruption for breast and colorectal cancer are substantial. For cervical cancer, the disruption had less influence. Furthermore, we showed that the size of the burden will be influenced by the restart strategy, whereby catching up on the missed screening activity would have the smallest effects on incidence and mortality, but the biggest effect on screening capacity. The other investigated restart strategies required a screening capacity similar to undisrupted screening. Among these, the cancer incidence and cancer-specific mortality were most favourable when screening was continued after the stopping age to allow for a similar number of screening rounds for the target population as without disruption.

The overall patterns in effects of the restart strategies were similar for the three cancer sites, but the effect sizes were different. The effects on incidence were the largest for breast cancer, smaller for colorectal cancer, and minimal for cervical cancer. These differences in effect size are caused by the difference in absolute cancer incidence, screening interval, and/or dwelling time between the cancer sites. In case of a shorter interval between screen tests, the relative increase in waiting time for the next round due to a six months disruption

is larger. Because of a relative lower incidence, longer screening interval, and larger dwelling time, the effects of the disruption and the restart strategies on cervical cancer incidence were small. It was remarkable that the cancer-specific mortality in colorectal cancer was much higher in the strategies in which the stopping age was not increased ('everyone delay' and 'first rounds no delay') than in the strategies that did increase the stopping age ('continue after stopping age' and 'catch-up after stop'). These differences can be explained due to the fact that in colorectal cancer all delayed individuals missed their last screening round in the 'everyone delay' and 'first rounds no delay' strategy. In case of breast cancer screening, due to a disruption of six months out of an interval of 24 months, one out of four individuals missed their last screening round (since we assumed screening appointments to be planned based on postal code instead of date of birth). In case of cervical cancer screening, only the additional screen at age 65 was omitted which was only offered to women who tested hrHPV positive at age 60. Therefore, the difference between the 'everyone delay' and 'continue after stopping age' strategies is bigger for colorectal than for breast and cervical cancer screening.

Nation-wide organised cancer screening programmes are known to reduce inequality between individuals with different socio-economic status.[19] To maintain this after a screening disruption, it is important that the restart of screening activity is well organised. The feasibility of the four restart strategies depends on the capacity available and the way screening programmes are set up in a country or region. In 2017, 68% of European countries indicated a limited capacity of the screening programme.[20] The limitations differed from a shortage of screening personnel to limitations in screening materials, lab capacity, follow-up tests, and insufficient financial resources. In the Netherlands, the breast cancer screening capacity is limited for primary screens due to a shortage of screening unit personnel, whereas the colorectal cancer screening capacity is limited by the colonoscopy capacity.[16,21] The specific limitations determine whether a country or region is able to reach the required capacity for the investigated restart strategies. Furthermore, practical issues can arise based on the way a screening programme is set up. For example, a programme with a fixed number of mobile breast cancer screening units is not able to catch-up disrupted screening and continue the originally scheduled screens at the same time for two different locations. Also, cervical cancer screening programmes can have limitations in analysing the hrHPV samples, because the lab equipment might be used for COVID-19 testing.

The results in this study were based on the screening situation in the Netherlands. In absolute numbers (based on the increase in incidence rate), the results estimated 145 additional breast cancer deaths, 13 additional cervical cancer deaths, and 307 additional colorectal cancer deaths between 2020 and 2030 for the 'continue after stopping age'

strategy compared to undisrupted screening. Despite the additional deaths compared to a situation without screening disruption, the screening programmes were estimated to still prevented 12 537 breast cancer, 2 655 cervical cancer, and 14 190 colorectal cancer deaths in this period in the Netherlands. This study did not investigate the effects of the disruption and the restart strategies on the amount of overdiagnosis. However, we expect that overdiagnosis will be lower for the first screening round after the disruption due to the increased screening interval. Furthermore, we expect that overdiagnosis can increase in the restart strategies which increase the stopping age, but we expect this increase to be small, because the stopping age was only increased by six months.

We expect that the capacity, incidence and mortality rates can be applied to other countries or regions with comparable screening strategies. For countries with significant differences in screening programmes compared to the Dutch programme, the effects of the disruption and the restart strategies can differ. For example, an upper age limit of 69 for breast cancer screening instead of 75 leads to a smaller population eligible for screening. Therefore, a smaller population is affected by the screening disruption, leading to smaller effect sizes. Next to that, for an annual screening interval in colorectal cancer screening instead of a biennial interval, the disruption becomes proportionately larger which can lead to larger effect sizes. Also, the use of a different screening test can influence whether the effects found are applicable to other countries. For example, the use of a cytology test only in cervical cancer screening instead of a combination of hrHPV and cytology tests can lead to different effect sizes. Especially in countries with opportunistic screening, the effects of a screening disruption are expected to differ a lot. Next to that, differences in results may be expected for countries or regions with a different population composition or a different population risk to develop breast, cervical, or colorectal cancer.

In practice, the Dutch breast cancer screening was disrupted for three months, cervical cancer screening for three and a half months, and colorectal cancer for two months. Sensitivity analyses showed that a screening disruption of three months led to smaller effect on capacity, incidence, and mortality. However, the programmes were not able to restart at full capacity due to hygiene and safety restrictions. Therefore, a part of the population will have a longer screening delay than the duration of the disruption. In the case of a 3-month disruption followed by six months with 50% capacity, nearly all screens will be delayed for six months, which implies the effects are comparable to a 6-month disruption followed by full capacity.

An important strength of this analysis is the timely response to the current screening situation and the use of well-validated models. However, this study also has some limitations. In the models, it was assumed that attendance to the screening programmes

was equal to the attendance rates before the screening disruption. In case attendance rates decrease after the disruption, we expect required capacity to be lower and cancer-specific mortality to be higher. Also, it was assumed that the screening programmes did not face further hygiene or safety restrictions because of the COVID-19 pandemic as soon as the screening disruption was over. In case of additional hygiene and safety restrictions after the disruption, the available capacity is expected to be low. This low capacity can lead to longer delays in screening for part of the population resulting in higher cancer-specific mortality rates. Furthermore, the assumption was made that other cause mortality did not change due to the COVID-19 pandemic, although it can be expected that it has an effect on mortality, especially in older age groups. We expect that cancer-specific mortality rates will be slightly lower if a higher other cause mortality is taken into account.

Notwithstanding these limitations, this study provides an important first peek in the potential impact of the screening disruptions on resource requirements and long-term benefits of existing screening programmes. It underlines the importance of careful consideration of the restart strategy to mitigate the negative impact of these disruptions. At the moment, this has become an important topic, because many countries were strained to disrupt their screening programmes due to the COVID-19 pandemic. This study provides well-grounded estimates on the requirements and effects of screening restart strategies for policy makers of national or regional cancer screening organisation so they can make informed decisions how to restart their screening programmes.

In conclusion, this study found that catching up on the delayed screening activity would result in the smallest effects on cancer incidence and cancer-specific mortality. However, this restart strategy requires a very high screening capacity in a short time period. A restart strategy in which all screening is delayed and the stopping age is increased requires a screening capacity similar to a situation without screening disruption and results in minimal effects on incidence and mortality.

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Authors' contributions

LK conceptualisation, analyses, investigation, methodology, software, visualisation, writing draft. SK conceptualisation, software, analyses, investigation, methodology, visualisation, reviewing draft. LdJ conceptualisation, software, analyses, investigation, methodology, visualisation, reviewing draft. EJ conceptualisation, methodology, reviewing draft. EP methodology, reviewing draft. EH conceptualisation, methodology, reviewing draft. NvR conceptualisation, methodology, reviewing draft. IL conceptualisation, methodology, reviewing draft. IdK conceptualisation, methodology, supervision, reviewing draft.

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Data availability

Detailed modelling results are available upon request.

Conflict of interest

The authors declare no conflict of interest.

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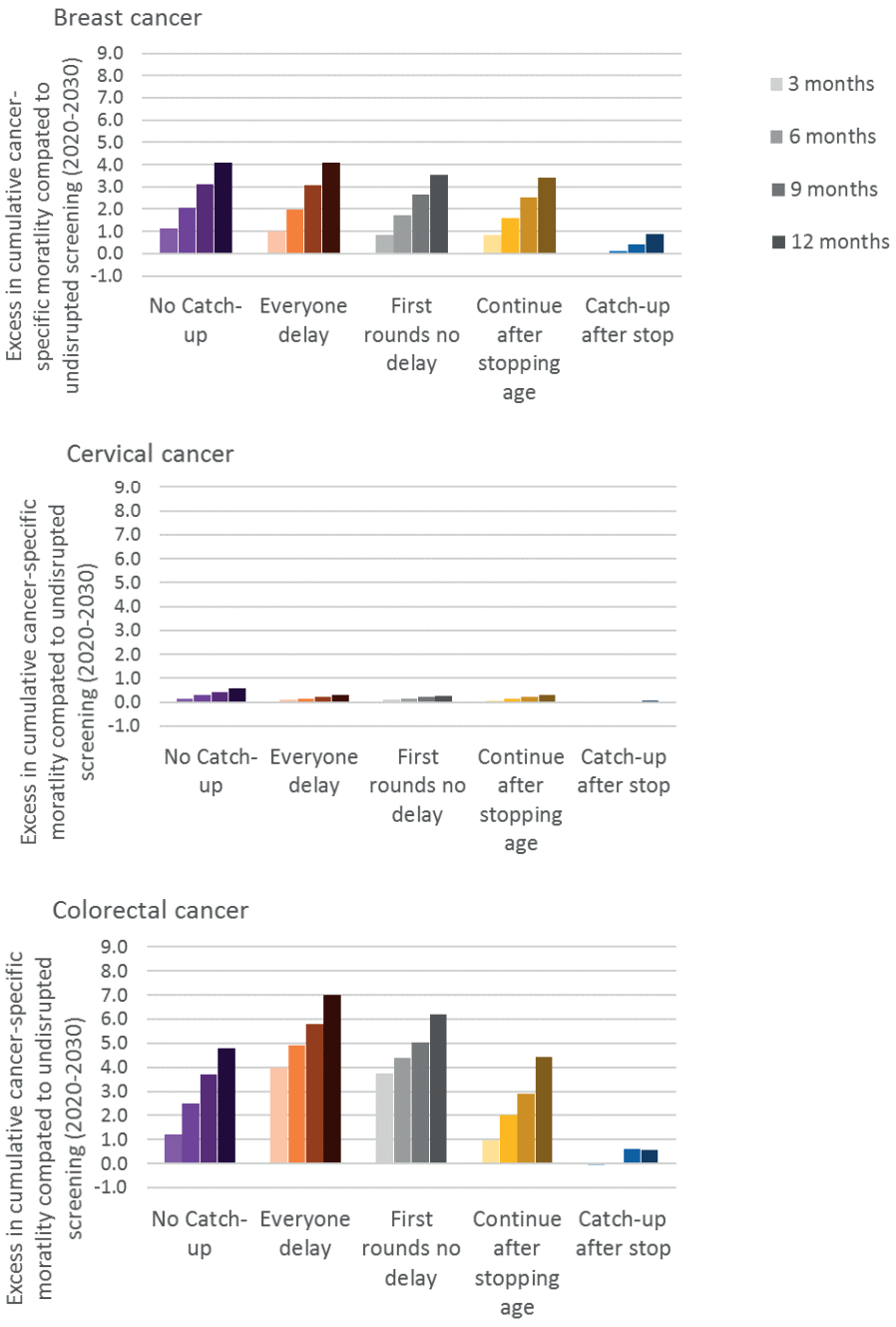
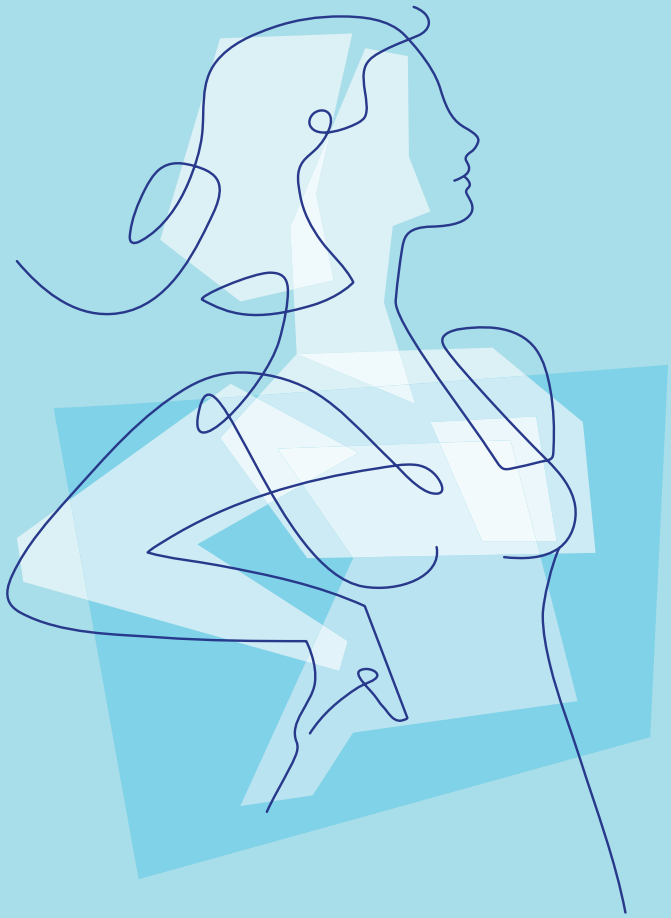
APPENDIX



Appendix Figure 1 Excess in cumulative cancer-specific mortality rate (per 100 000) between 2020 and 2030 for the different restart strategies after disruptions of 3, 6, 9, and 12 months for breast cancer, cervical cancer, and colorectal cancer



6

Finding the optimal mammography screening strategy: a cost-effectiveness analysis of 920 modelled strategies

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ABSTRACT

Breast cancer screening policies have been designed decades ago, but current screening strategies may not be optimal anymore. Next to that, screening capacity issues may restrict feasibility. This cost-effectiveness study evaluates an extensive set of breast cancer screening strategies in the Netherlands. Using the Microsimulation Screening Analysis-Breast (MISCAN-Breast) model, the cost-effectiveness of 920 breast cancer screening strategies with varying starting ages (40-60), stopping ages (64-84), and intervals (1-4 years) were simulated. The number of quality adjusted life years (QALYs) gained and additional net costs (in €) per 1,000 women were predicted (3.5% discounted) and incremental cost-effectiveness ratios (ICERs) were calculated to compare screening scenarios. Sensitivity analyses were performed using different assumptions. In total, 26 strategies covering all four intervals were on the efficiency frontier. Using a willingness-to-pay threshold of €20,000/QALY gained, the biennial 40-76 screening strategy was optimal. However, this strategy resulted in more overdiagnoses and false positives, and required a high screening capacity. The current strategy in the Netherlands, biennial 50-74 years, was dominated. Triennial screening in the age range 44-71 (ICER 9,364) or 44-74 (ICER 11,144) resulted in slightly more QALYs gained and lower costs than the current Dutch strategy. Furthermore, these strategies were estimated to require a lower screening capacity. Findings were robust when varying attendance and effectiveness of treatment. In conclusion, switching from biennial to triennial screening while simultaneously lowering the starting age to 44 can increase benefits at lower costs and with a minor increase in harms compared to the current strategy.

INTRODUCTION

Breast cancer is the most prevalent cancer and leading cause of cancer-related mortality amongst women worldwide.[1] The first breast cancer screening programmes in Europe started in the late 1980s and have been shown to reduce breast cancer mortality significantly.[2,3] Currently, most European countries have implemented a screening programme, with some variety in starting and stopping ages, and screening intervals.[3] The cost-effectiveness of these screening strategies has been proven in multiple studies.[4] However, these studies only included a subset of possible alternative strategies.

An optimal screening strategy generates the best balance between benefits (e.g. life years gained (LYG)) and harms (e.g. overdiagnoses) at reasonable costs. Over the years, this balance between benefits and harms of breast cancer screening has been debated. Since implementation of screening, breast cancer risk factors increased and thereby the lifetime risk for women to be diagnosed with breast cancer increased.[5,6] It can be expected that this increased the population of women who benefit from breast cancer screening. In addition, both breast cancer screening and breast cancer treatment have improved (e.g. digital mammography instead of film-based mammography and more efficient adjuvant treatments), which has led to a decrease in breast cancer mortality.[7-9] These changes might have shifted the harm-benefit balance of breast cancer screening, implying that current screening strategies may not be optimal anymore.

The decision to implement a certain screening strategy is also based on the resources available. More than half of European countries face a limited capacity of screening due to a lack of human, physical, or financial resources.[10] This may lead to a maximum number of screening tests that can be performed in a country or region. This restriction can, in turn, decrease invitation coverage, narrow the age range of women invited, increase waiting time between tests and results, or increase intervals between screening rounds.[11,12] Therefore, it is important to take capacity restrictions into account when possible changes in screening strategies are investigated.

In 1990, biennial breast cancer screening was implemented in the Netherlands for women aging 50-69 years. This age range was extended to 74 in 1998. The current programme invites women aged 50-74 every two years. However, it is uncertain whether this is still the most optimal strategy. In addition, the Dutch breast cancer screening programme faces capacity issues which makes investigation of less intensive alternatives of interest and timely.[11] Therefore, this study aimed to investigate the cost-effectiveness of an extensive set of breast cancer screening strategies which differ in starting age, stopping age, and screening interval.

MATERIALS AND METHODS

The effects of different screening strategies were predicted using the MIcrosimulation SCreening ANalysis-Breast (MISCAN-Breast) model.[7] MISCAN-Breast simulates individual life histories of women and, in a subset of them, the natural history of breast cancer. In addition, breast cancer screening programmes can be simulated to determine the effects of the screening protocol on breast cancer incidence, mortality and Quality Adjusted Life Years (QALYs). In the model, breast cancer starts with a pre-clinical ductal carcinoma in situ (DCIS) that can progress to invasive stages T1A, T1B, T1C, and T2+, respectively. A tumour can become screen-detected (in presence of screening), clinically detected (in presence of symptoms), or can progress to the next preclinical stage (Appendix figure 1).[13]

Model parameters and assumptions

The MISCAN-Breast model was updated with data on breast cancer treatment up to 2013 and previously calibrated for the natural history of breast cancer, and breast cancer survival rates with data up to 2015 (Appendix page 2).[14]

We simulated a cohort of 10 million women at average risk of developing breast cancer in which the tumour growth rate was distributed over a range including aggressive and slow growing rates. All women were born on the 1st of January in 1980 and lifetables were based on data from Statistics Netherlands with a maximal life expectancy of 100 years.[15] Outcomes were calculated for the women from age 40 until death. In order to calculate the full potential of the screening strategies, attendance rates were set at 100%.

The screening protocol in the model was adjusted for each investigated screening strategy. The intervals of interest were annual, biennial, triennial and quadrennial. Next to that, the start and stop ages were varied with a maximum of 10 years around the current screening ages in the Netherlands: starting age 40-60, and stopping age 64-84. This resulted in 920 different screening protocols, including no screening. Screening appointments were simulated to occur on the day the women reached the age at which an appointment was scheduled according to the protocol.

For each screening strategy, the number of invitations, screening mammograms, breast cancers detected by mode of detection (stage and age specific), total life-years, life-years with diagnosis (stage and age specific), and breast cancer deaths were predicted. From these predictions, number of breast cancer deaths averted, overdiagnoses, false positives, QALYs, and additional costs were calculated.

Cost-effectiveness analyses

A healthcare payer perspective was adopted and direct medical costs were calculated, including costs of screening, diagnostics, and treatment. Data on costs and utilities were based on Geuzinge et al. and indexed to 2018 (Appendix: page 2 and Table 1).[16] False positive (FP) findings were calculated using screen-detected cancers from the model output and the positive predicted value (PPV) of recall. PPVs were specified by age (<50 and ≥50) and screening interval (Appendix page 2).

QALYs and costs were calculated for a situation with screening compared to no screening. Both effects and costs were discounted at 3.5% per year from 2020 to take time preferences into account.[17]

The screening strategies were ranked according to their costs (lowest to highest). Subsequently, incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in costs by the difference in QALYs between a strategy and its precursor in the ranking. Therefore, the ICER reflects the costs required to gain one QALY compared to the previous strategy. ICERs were not calculated for strategies that were dominated by another strategy (i.e. another strategy gained more QALYs and required less costs). The ICERs were compared to a conservative willingness to pay (WTP) threshold of €20,000 per QALY gained.[18] Strategies that did not exceed this threshold were considered to be cost-effective.

International strategies

Within Europe, breast cancer screening programmes differ in ages covered and screening interval.[2] The majority of these strategies were present in the set of 920 strategies which were modelled as part of the cost-effectiveness analyses. In these model calculations, the screening strategies were applied to the situation in the Netherlands (i.e. Dutch population size, screening parameters, and breast cancer treatment effectiveness), preserving the assumption of 100% attendance. To evaluate the effectiveness of international strategies on the situation in the Netherlands, these strategies are plotted together with the efficiency frontier.

Capacity analyses

To evaluate the impact of different screening scenarios on screening capacity, the MISCAN-Breast model was also used to simulate the effects of a subset of strategies of interest using a full population instead of a single cohort. The population that was simulated represented the Dutch female population based on population numbers until 2020 and population prognoses for the years after 2020.[19] In this simulation, age-specific participation rates were used as described in the sensitivity analyses. All other model

parameters remained equal to the previous cohort simulations. The outcomes of interest produced by these population simulations was the average number of screens performed for the years 2020-2030.

Sensitivity analyses

Sensitivity analyses were performed using LYG as effect measure to calculate ICERs, age-specific participation rates, and assumptions on current adjuvant treatment use. The age-specific participation rates were based on participation rates from the Dutch breast cancer screening programme between April 2017 and April 2019 (Appendix Table 2). Participation rates for ages below age 50 and after age 75 were extrapolated. Estimates for breast cancer treatment use between 2013 and 2020 were made based on trends in treatment changes between 2004 and 2011 (Appendix Table 3).

Additionally, separate ICERs were calculated for all strategies in which the starting age was at least 45, because the International Agency for Research on Cancer (IARC) found that there is sufficient evidence that breast cancer screening reduces mortality in women aged 50-74 and that the evidence for women aged 45-49 was nearly sufficient.[20,21]

RESULTS

Without screening, the model estimated 149 breast cancer diagnoses and 49 breast cancer deaths per 1,000 40-year old women who were followed over their lifetime (no discount). Biennial screening for ages 50-74 (current strategy) was estimated to avert 16 breast cancer deaths (33%) and gain 231 QALYs per 1,000 women compared to no screening. However, this strategy also led to 5 overdiagnoses and 187 FP screening results. When discounting, this would result in 61.7 QALYs gained and €374,763 additional costs, resulting in €6,074 per QALY gained.

Figure 1 shows the cost-effectiveness curve of all investigated screening strategies (3.5% discounted). The efficiency frontier shows which strategies were efficient. Although the current strategy was close to the efficiency frontier, it was dominated. The efficiency frontier consisted of strategies with all four investigated screening intervals. However, all annual screening strategies were above the WTP threshold of €20,000.

Incremental cost-effectiveness

Table 1 shows the model estimates for the current strategy and the screening strategies on the efficiency frontier. According to the conservative WTP threshold of €20,000 per QALY gained, biennial screening for the ages 40-76 would be the preferred strategy with an

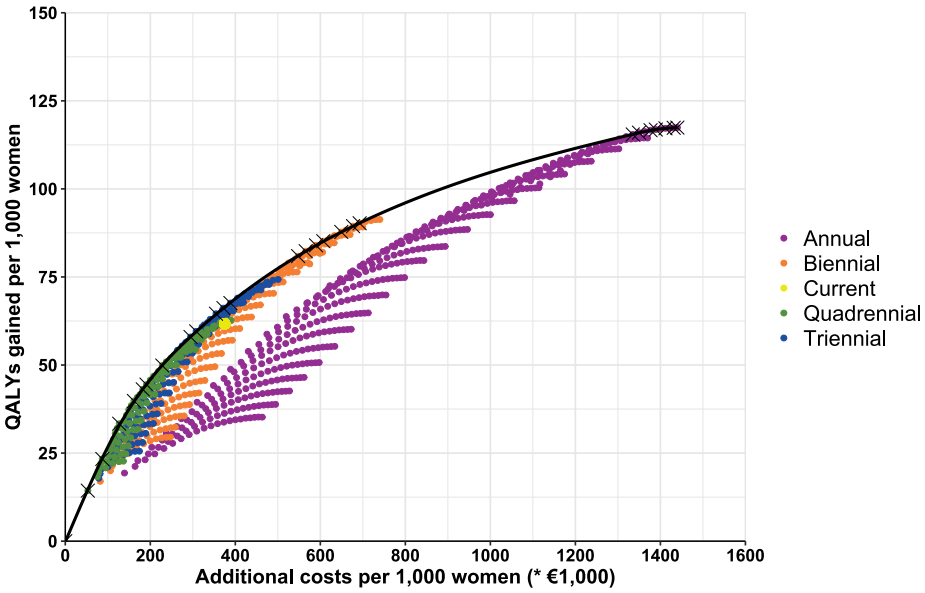

Figure 1 Cost-effectiveness curve for scenarios with starting ages between 40 and 60 and stopping ages between 64 and 84, including efficiency frontier

ICER of €19,164 per QALY gained (3.5% discounted). This strategy resulted in more breast cancer deaths averted (6.6 vs. 4.9 per 1,000 women) and more QALYs gained (90.2 vs. 61.7) than current screening. On the other hand, there were more overdiagnoses, (7.3 vs. 5.8 per 1,000 women), many more false positives (168 vs. 89), and additional costs were higher (€692,550 vs. €374,763).

To achieve at least the same number of QALYs as the current strategy, triennial screening for the ages 44-71 was the first strategy on the frontier. This strategy gained more QALYs than the current strategy (64.6 vs. 61.7 per 1,000 women), and had lower additional costs (€354,556 vs. €374,763). This resulted in an ICER of €9,321 per QALY gained. In addition, the number of overdiagnoses was lower (5.2 vs. 5.8 per 1,000 women) while the number of false positives was higher (99 vs. 89) compared to the current strategy. Another strategy of interest could be triennial screening for the ages 44-74. The additional costs of this strategy were approximately the same as the current strategy (€372,241 vs. €373,763 per 1,000 women), while the amount of QALYs gained increased (61.7 vs. 66.2), the number of overdiagnoses was slightly lower (5.7 vs. 5.8), and the number of false positives was higher (103 vs. 89). In this strategy, the ICER was estimated to be €11,103 per QALY gained.

International strategies

Figure 2 shows the effects of breast cancer screening strategies implemented by different European countries if they would be implemented in the Netherlands together with the

Table 1 Discounted model estimates of the number of breast-cancer (BC) deaths averted, overdiagnoses, QALYs gained, and additional costs (€) per 1,000 women compared to no screening with percentage change compared to the current strategy (B50-74). The table includes the current strategy and strategies on the efficiency frontier with corresponding ICERs.

Strategy	BC deaths averted		Overdiagnoses		False positives		QALYs gained		Additional costs (€)		ICER
Biennial 50-74	4.9	-	5.8	-	89	-	61.7	-	374,762	-	Dominated
Quadrennial 60-64	1.3	-75%	1.7	-72%	18	-80%	14.3	-77%	53,050	-86%	3,699
Quadrennial 56-64	1.9	-62%	2.2	-62%	25	-71%	23.3	-62%	87,100	-77%	3,787
Quadrennial 52-64	2.5	-50%	2.7	-54%	32	-64%	33.3	-46%	126,875	-66%	3,974
Quadrennial 50-66	3.0	-40%	3.2	-45%	38	-57%	39.8	-36%	161,450	-57%	5,356
Quadrennial 50-70	3.4	-32%	3.9	-33%	44	-50%	43.1	-30%	182,304	-51%	6,327
Quadrennial 49-69	3.4	-31%	3.8	-34%	51	-43%	44.4	-28%	191,039	-49%	6,508
Quadrennial 47-71	3.8	-23%	4.3	-25%	62	-30%	49.9	-19%	228,179	-39%	6,856
Triennial 47-71	4.4	-11%	4.9	-16%	83	-7%	58.0	-6%	294,724	-21%	8,212
Triennial 46-70	4.4	-11%	4.8	-17%	89	0%	59.6	-4%	307,927	-18%	8,250
Triennial 44-71	4.7	-4%	5.2	-11%	99	11%	64.6	5%	354,556	-5%	9,321
Triennial 44-74	5.0	1%	5.7	-3%	103	17%	66.2	7%	372,241	-1%	11,103
Triennial 43-73	5.0	1%	5.6	-4%	109	23%	67.6	9%	388,503	4%	11,269
Biennial 43-71	5.8	18%	6.1	5%	142	60%	80.9	31%	547,816	46%	11,963
Biennial 43-73	6.0	22%	6.5	11%	146	65%	82.3	33%	565,623	51%	12,672
Biennial 42-72	6.0	22%	6.4	10%	150	69%	84.0	36%	589,839	57%	14,502
Biennial 42-74	6.2	26%	6.8	16%	154	74%	85.2	38%	606,977	62%	14,684
Biennial 41-75	6.4	29%	7.0	21%	162	82%	87.8	42%	649,316	73%	16,162
Biennial 40-74	6.4	30%	6.9	19%	165	86%	89.4	45%	676,927	81%	16,716
Biennial 40-76	6.6	33%	7.3	25%	168	90%	90.2	46%	692,550	85%	19,164
Annual 40-75	8.2	66%	8.6	47%	259	192%	115.5	87%	1,334,950	256%	25,478
Annual 40-76	8.3	68%	8.8	50%	261	195%	116.0	88%	1,349,662	260%	29,090
Annual 40-78	8.4	70%	9.1	57%	266	200%	116.7	89%	1,376,779	267%	39,319
Annual 40-79	8.5	72%	9.3	60%	268	202%	116.8	89%	1,389,199	271%	63,919
Annual 40-81	8.6	73%	9.7	66%	271	206%	117.2	90%	1,411,796	277%	65,630
Annual 40-83	8.6	74%	10.0	71%	274	209%	117.3	90%	1,431,299	282%	132,200
Annual 40-84	8.6	75%	10.1	73%	275	211%	117.4	90%	1,439,916	284%	133,050

* The strategy with a light grey background is not on the efficiency frontier, but included because it is the current strategy. The strategy with a dark grey background is the optimal strategy based on a WTP threshold of €20,000 per QALY gained. The other strategies with a grey background are candidate strategies based on more favourable QALYs and costs compared to the current strategy.

efficiency frontier from Figure 1. None of the internationally implemented strategies were on the efficiency frontier, although all strategies were very close.

Capacity analyses

Population simulations were performed for the strategies biennial 50-74, biennial 40-76, triennial 44-71, and triennial 44-74. Biennial screening for ages 40-76 was estimated to

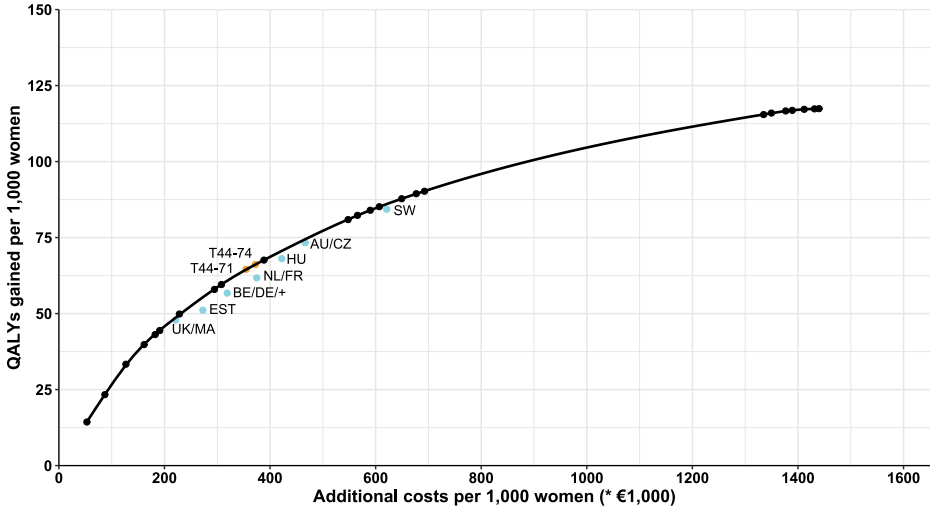

Figure 2 Effects of internationally implemented strategies assuming 100% attendance. United Kingdom (UK) and Malta (MA) triennial 50-69; Estonia (EST) and biennial 50-64; Belgium (BE), Germany (DE), Poland, Cyprus, Denmark, Finland, Latvia, Lithuania, Luxembourg, Norway, Poland, Slovenia and Switzerland biennial 50-69; the Netherlands (NL) and France (FR) biennial 50-74; Hungary (HU) biennial 45-65; Austria (AU) and Czech republic (CZ) biennial 45-69; Sweden (SW) biennial 40-69

result in 34% more screens being performed per year compared to the current screening strategy (Table 2). Triennial screening for ages 44-71 or for ages 44-74 would lead to a reduction in the number of screens performed of 22% and 17%, respectively.

Table 2 Number of screens performed per year for the strategies of interest

	# screens per year	% difference compared to biennial 50-74	ICER*
Biennial 50-74	1,057,896	-	dominated
Biennial 40-76	1,416,427	+34%	19,164
Triennial 44-71	820,636	-22%	9,321
Triennial 44-74	880,759	-17%	11,103

* the ICERs were obtained from Table 1 and were based on calculations including all strategies on the efficiency frontier.

Sensitivity analyses

When looking at LYG as effective measure instead of QALYs gained, the same three strategies were of interest (Appendix table 4). In all three strategies the amount of LYG was increased compared to the amount of LYG in the current strategy.

Taking into account age-specific attendance rates in all modelled screening strategies decreased the number of breast cancer deaths averted, overdiagnoses, false positives, QALYs gained, and additional costs (Table 3). This also slightly changed which strategies were present on the efficiency frontier and the accompanying ICERs (Appendix page 7).

Table 3 Discounted model estimates for sensitivity analyses using age-dependent attendance rates on the number of breast-cancer (BC) deaths averted, overdiagnoses, QALYs gained, and additional costs (€) per 1,000 women compared to no screening with percentage change compared to the current strategy (B50-74). The table includes the current strategy and strategies on the efficiency frontier with corresponding ICERs.

Strategy	BC deaths averted		Overdiagnoses		False positives		QALYs gained		Additional costs (€)		ICER
Biennial 50-74	4.1	-	4.8	-	73	-	51.0	-	293,414	-	Dominated
Quadrennial 60-64	1.0	-76%	1.3	-73%	14	-81%	11.5	-77%	41,468	-86%	3,611
Quadrennial 56-64	1.5	-63%	1.8	-63%	20	-72%	18.9	-63%	68,621	-77%	3,652
Quadrennial 52-64	2.0	-52%	2.1	-55%	25	-66%	26.3	-48%	99,199	-66%	4,117
Quadrennial 51-67	2.3	-42%	2.6	-45%	30	-58%	30.7	-40%	121,794	-58%	5,131
Quadrennial 51-71	2.6	-35%	3.1	-35%	35	-52%	33.1	-35%	136,537	-53%	6,196
Quadrennial 50-70	2.7	-34%	3.1	-35%	35	-52%	34.2	-33%	143,159	-51%	6,339
Quadrennial 47-71	3.0	-27%	3.4	-29%	48	-34%	38.9	-24%	175,861	-40%	6,900
Triennial 48-69	3.2	-21%	3.5	-26%	60	-17%	43.2	-15%	205,425	-30%	6,963
Triennial 48-72	3.5	-15%	3.9	-17%	65	-11%	45.0	-12%	219,527	-25%	7,701
Triennial 45-72	3.7	-8%	4.1	-13%	77	6%	49.9	-2%	263,080	-10%	8,904
Biennial 44-72	4.7	15%	5.0	6%	109	49%	63.6	25%	406,206	38%	10,404
Biennial 44-74	4.8	18%	5.3	12%	112	54%	64.6	27%	418,729	43%	13,073
Biennial 43-73	4.8	19%	5.3	11%	120	65%	65.9	29%	436,779	49%	13,668
Biennial 43-75	5.0	22%	5.5	16%	123	69%	66.8	31%	448,488	53%	14,007
Biennial 42-74	5.0	23%	5.5	15%	121	66%	68.0	33%	466,350	59%	14,627
Biennial 40-74	5.1	27%	5.6	17%	128	76%	71.2	40%	516,777	76%	15,710
Biennial 40-76	5.3	29%	5.9	23%	131	80%	71.8	41%	527,777	80%	17,784
Annual 42-73	6.5	60%	6.8	42%	197	171%	90.6	78%	898,319	206%	19,719
Annual 42-74	6.6	62%	6.9	46%	199	174%	91.1	79%	910,480	210%	21,896
Annual 42-75	6.7	64%	7.1	49%	202	177%	91.7	80%	921,916	214%	21,997
Annual 41-73	6.6	63%	6.8	44%	204	181%	92.8	82%	947,557	223%	22,208
Annual 41-75	6.8	67%	7.2	51%	209	187%	93.9	84%	971,196	231%	22,306
Annual 40-75	6.9	69%	7.3	53%	216	197%	96.1	88%	1,022,070	248%	23,364
Annual 40-77	7.0	72%	7.6	60%	220	202%	96.8	90%	1,042,553	255%	28,570
Annual 40-81	7.2	76%	8.2	72%	226	210%	97.5	91%	1,075,099	266%	43,734
Annual 40-82	7.2	77%	8.3	74%	227	212%	97.6	91%	1,081,621	269%	80,786
Annual 40-84	7.2	78%	8.5	78%	229	214%	97.7	92%	1,092,504	272%	174,927

* The strategy with a light grey background is not on the efficiency frontier, but included because it is the current strategy. The strategy with a dark grey background is the optimal strategy based on a WTP threshold of €20,000 per QALY gained. The other strategies with a grey background are candidate strategies based on more favourable QALYs and costs compared to the current strategy.

When alternative assumptions on current adjuvant treatment use were used, the number of breast cancer deaths averted, overdiagnoses, false positives, and QALYs gained were slightly lower (Appendix table 5). On the other hand, the additional costs slightly increased. In addition, the strategies which were present on the efficiency frontier and

the accompanying ICERs slightly changed compared to the base case analyses (Appendix page 7).

If only strategies with starting ages between age 45 and 60 were included in the ICER calculations, different strategies appear on the efficiency frontier (Table 4). When considering the conservative WTP threshold of €20,000 per QALY gained, biennial screening for ages 45-75 would be optimal (ICER: 17,147). When comparing to the current strategy, the triennial 45-72 strategy would gain more QALYs (63.0 vs. 61.7 per 1,000 women) and have less additional costs (€340,815 vs. €374,763).

Table 4 Discounted model estimates for sensitivity analyses with starting ages ranging from age 45 to age 60 on the number of breast cancer (BC) deaths averted, overdiagnoses, QALYs gained, and additional costs (€) per 1,000 women compared to no screening with percentage change compared to the current strategy (B50-74). The table includes the current strategy and strategies on the efficiency frontier with corresponding ICERs.

Strategy	BC deaths averted		Overdiagnoses		False positives		QALYs gained		Additional costs (€)		ICER
Biennial 50-74	4.9	-	5.8	-	89	-	61.7	-	374,762	-	Dominated
Quadrennial 60-64	1.3	-75%	1.7	-72%	18	-80%	14.3	-77%	53,050	-86%	3,699
Quadrennial 56-64	1.9	-62%	2.2	-62%	25	-71%	23.3	-62%	87,100	-77%	3,787
Quadrennial 52-64	2.5	-50%	2.7	-54%	32	-64%	33.3	-46%	126,875	-66%	3,974
Quadrennial 50-66	3.0	-40%	3.2	-45%	38	-57%	39.8	-36%	161,450	-57%	5,356
Quadrennial 50-70	3.4	-32%	3.9	-33%	44	-50%	43.1	-30%	182,304	-51%	6,327
Quadrennial 49-69	3.4	-31%	3.8	-34%	51	-43%	44.4	-28%	191,039	-49%	6,508
Quadrennial 47-71	3.8	-23%	4.3	-25%	62	-30%	49.9	-19%	228,179	-39%	6,856
Triennial 47-71	4.4	-11%	4.9	-16%	83	-7%	58.0	-6%	294,724	-21%	8,212
Triennial 46-70	4.4	-11%	4.8	-17%	89	0%	59.6	-4%	307,927	-18%	8,250
Triennial 45-72	4.7	-5%	5.3	-10%	100	12%	63.0	2%	340,815	-9%	9,620
Biennial 45-71	5.5	12%	5.9	1%	128	45%	75.3	22%	485,671	30%	11,765
Biennial 45-73	5.7	16%	6.3	8%	133	50%	76.7	24%	503,538	34%	12,763
Biennial 45-75	5.9	19%	6.6	14%	137	54%	77.6	26%	519,870	39%	17,147
Biennial 45-77	6.0	21%	7.0	20%	140	58%	78.3	27%	534,735	43%	21,629
Annual 45-74	7.3	47%	7.7	32%	205	131%	97.9	58%	993,630	165%	23,500
Annual 45-76	7.4	50%	8.1	39%	210	137%	98.9	60%	1,023,878	173%	29,174
Annual 45-77	7.5	52%	8.3	43%	213	140%	99.3	61%	1,037,823	177%	35,320
Annual 45-78	7.6	53%	8.5	46%	215	142%	99.6	61%	1,050,976	180%	44,453
Annual 45-80	7.6	55%	8.8	52%	219	147%	100.0	62%	1,075,080	187%	53,111
Annual 45-81	7.7	55%	9.0	55%	220	148%	100.1	62%	1,085,994	190%	127,467
Annual 45-84	7.8	57%	9.5	62%	224	153%	100.3	62%	1,114,172	197%	136,768

* The strategy with a light grey background is not on the efficiency frontier, but included because it is the current strategy. The strategy with a dark grey background is the optimal strategy based on a WTP threshold of €20,000 per QALY gained. The other strategies with a grey background are candidate strategies based on more favourable QALYs and costs compared to the current strategy.

DISCUSSION

This is the first study to investigate the cost-effectiveness of an extensive set of breast cancer screening strategies varying in starting age, stopping age, and screening intervals. Using a conservative WTP threshold of €20,000 per QALY gained, biennial screening for ages 40-76 was preferred. This strategy resulted in more breast cancer deaths averted and QALYs gained than current screening. However, it required a 34% higher screening capacity per year than the current strategy. When taking into account capacity issues, less intensive alternative cost-effective strategies with comparable costs or QALYs as the current strategy were triennial screening for the ages 44-71 or 44-74. Thus, our results indicate that triennial screening with a lower starting age is a very good alternative, especially for countries facing capacity issues, because it can lead to more benefits at similar costs. We acknowledge that starting screening earlier is controversial, in particular before the age of 45, due to lack of evidence of screening effectiveness. Therefore, sensitivity analyses were performed in which the starting age of screening was at least 45 which resulted in triennial screening for the ages 45-72 to be a good alternative to current screening.

Our study had some limitations. One is the need to make assumptions, because it is still largely unknown how some parameters change for different screening intervals and for a population of women under 50 and over 74.[2,22] Especially the screening sensitivity, effectiveness and PPV for women under the age of 45 is largely unknown.[20] Therefore, we assumed these factors to be the same as for women aged 45-50. Benefits (LYG) in young women might be higher due to longer remaining life expectancy, but harms (FPs) larger, due to higher breast density.[23] We assumed the PPV for women under the age of 50 to be lower than in women over 50. However, since the PPV in the Netherlands is relatively high compared to other countries, we expect that in countries with a lower PPV, screening for younger ages may be less favourable.[24] Another limitation is the choice to not include hybrid screening strategies (i.e. different intervals for different age groups). Combining different intervals by age group may lead to a better harm-benefit balance for each specific age group. However, including hybrid strategies in the analyses would lead to a major increase in possible strategies.

The chosen WTP threshold of €20,000 per QALY gained is conservative compared to other studies which use WTP thresholds of €30,000 per QALY gained or more.[4,25-27] However, even when using this conservative threshold, already a rather intensive screening strategy was found to be optimal, with increased harms and a higher required capacity than the current screening strategy. Using a WTP threshold of €30,000 will indicate more intensive screening strategies to be optimal (i.e. annual screening for ages 40-76) with more harms and a higher required capacity. Another assumption we made was 100% screening

attendance. Even though an attendance rate of 100% is practically impossible and ethically undesirable, this assumption made it possible to estimate the potential of each screening strategy and it allowed for a comparison to the literature. Another reason to model 100% attendance was to prevent the preferred strategy to be too intensive for women who choose to comply completely. To estimate more realistic effects of the screening strategies, sensitivity analyses were performed with Dutch age-specific attendance rates. Attendance rates may differ between different screening intervals, however, a lack of participation estimates for different screening intervals made it impossible to incorporate this in the sensitivity analyses. In addition, screening appointments were assumed to take place on the day the women reached the age at which an appointment was planned according to the strategy instead of spread over the interval between screening ages. Accordingly, the average screening age will slightly increase if a modelled strategy is implemented.

Strengths of our study include the use of a well-established, calibrated, model and the evaluation of an extensive set of scenarios. So far, most cost-effectiveness studies on breast cancer screening have only investigated the effects of a restricted number of screening strategies. For example, a study in Spain modelled 20 strategies which found that starting screening at age 50 is preferred over age 40 or 45, and stopping at age 74 is preferred over age 69.[28] Furthermore, they concluded that the ICER was much higher for annual than for biennial strategies. However, this study only included annual and biennial strategies, which could have led to underestimation of ICERs.[29] A Slovenian modelling study investigated the cost-effectiveness of 36 breast cancer screening strategies and found that screening triennially for the ages 40-80 would be optimal (ICER: €13,352 per QALY gained).[26] However this study included intervals of a maximum of three years, which possibly omitted efficient strategies with longer intervals.[29] Next to that, an American study modelled the cost-effectiveness of 66 strategies including five-year intervals, however, four-year intervals were left out, which may cause a kinked efficiency frontier.[29,30] This study did not select an optimal strategy, however, the calculated ICERs were much higher than ICERs of comparable strategies in our analysis. Another Spanish study did investigate an extensive set of 2.625 screening strategies in which 24 strategies were uniform for the total population and 2,601 were risk-based.[31] This study found risk-based screening to be more efficient than uniform strategies. They proposed risk-based screening including three and five year intervals for low risk groups and annual screening for high risk groups. However, just like the American study, four-year intervals were not investigated. Next to that, all four studies only included round starting and stopping ages (40, 45, 50 etc.) which results in a subset of possible screening strategies. Although, for implementation round numbers seem more logical and feasible, by only investigating a subset of strategies the calculations of the ICERs can be incomplete. This could lead to misidentification of an inefficient strategy as optimal.[29]

The breast cancer screening strategies that are currently implemented in the Netherlands and in other European countries were not on the efficiency frontier. This raises the question of why they were implemented. Most screening programmes were implemented more than 20 years ago. Back then, many countries based their decisions mainly on randomised controlled trials instead of extensive cost-effectiveness studies. Partly because it was not possible to calculate or simulate the effects of a large set of strategies because of the computational power. Also, although there are still uncertainties about screening in women before the age of 50, more knowledge has been gained in the last decades. This is also partly reflected in the newest breast cancer guidelines on screening ages and frequencies by the European Commission Initiative on Breast Cancer (ECIBC) which suggests no screening between the ages 40-44, biennial or triennial screening for the ages 45-49, biennial screening for the ages 50-69, and triennial screening for the ages 70-74.[32] These recommendations, however, did not consider cost-efficiency nor resources and capacity. On top of these methodological issues, changes in breast cancer incidence, screening modalities, and treatment options may have shifted optimal screening towards triennial intervals and starting at younger ages becoming more beneficial. Although, differences in incidence, treatment, and population characteristics between countries could lead to different strategies being optimal than the ones found in the current study using the Dutch situation. Furthermore, the strategies that were present on the efficiency frontier are currently not implemented anywhere else. Which means that there is no information yet on the true effectiveness of these strategies when implemented.

Although performed from a Dutch perspective, our findings might be relevant for other countries as well, especially those facing capacity issues.[10-12] The COVID-19 pandemic has led to a disruption or restriction in breast cancer screening in many countries, raising the question of how to restart screening programmes.[33] Combined with capacity limitations, this may encourage policy makers to consider programme changes. This study can inform these policy makers about the cost-effectiveness and some of the benefits and harms of alternative screening strategies. The alternative triennial screening strategies were estimated to require a lower screening capacity than the current Dutch biennial screening programme. Implementing one of these strategies in the Netherlands can be expected to reduce the personnel capacity problems reported by the Dutch National Institute for Public health and Environment (RIVM).[11] However, before a new programme can be implemented, additional factors need to be taken into account, such as screening harms, logistical factors, population equity, and level of acceptance by the target population. Furthermore, the time and costs of the implementation processes need to be considered. By measuring QALYs, the effects of multiple harms were incorporated; however policy makers may weigh certain harms differently. The triennial strategies were estimated to slightly decrease the amount of overdiagnosis, the amount of false positives increased,

and one of the strategies was estimated to avert fewer breast cancer deaths than the current strategy. Furthermore, triennial strategies may lead to more interval cancers than biennial screening strategies.

In conclusion, we found that the current Dutch breast cancer screening strategy and strategies applied in many other European countries were not the most cost-effective options and can be improved. A quite more intensive screening scenario of screening biennially for the ages 40-76 years was found to be optimal. More realistically, restricting the costs and the number of screens, we found that triennial screening for ages 44-71 or 44-74 would be the preferred breast cancer strategy.

Conflict of interest

The authors have declared no conflicts of interest.

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Data Availability statement

Data used as input for the MISCAN-Breast model can be requested from the primary source (Appendix Table 1). Model outcome data can be made available upon reasonable request.

Author contributions

LK: Conceptualisation, data curation, formal analysis, investigation, methodology, validation, visualisation, writing – original draft. VS: Conceptualisation, data curation, methodology, writing – review & editing. EH: Conceptualisation, data curation, validation, writing – review & editing. HdK: Conceptualisation, funding acquisition, supervision, validation, writing – review & editing. NvR: Conceptualisation, data curation, funding acquisition, methodology, supervision, validation, writing – review & editing. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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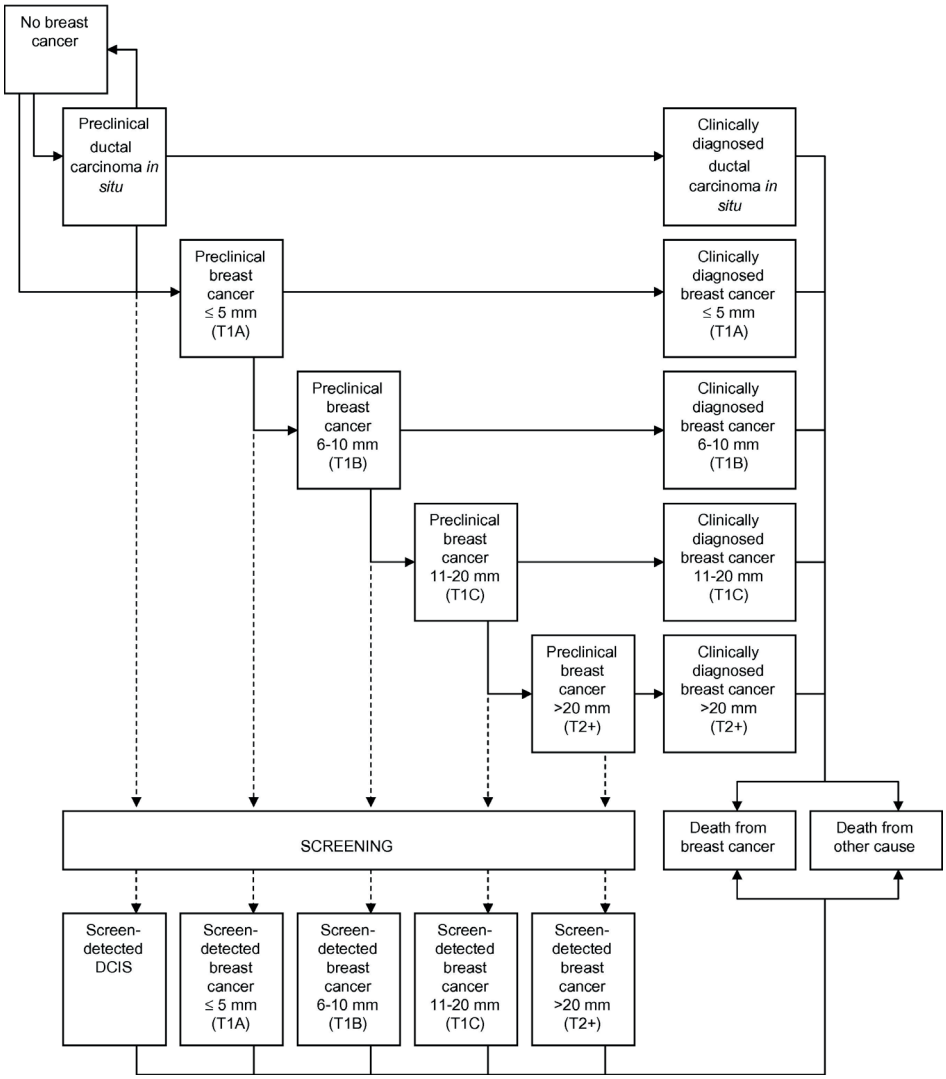
APPENDIX

Appendix figure 1



Appendix figure 5 MISCAN-Breast transitions (de Gelder et al. (2009)[1])

Appendix page 2

Calibration of MISCAN-Breast

During the recent calibration or MISCAN-Breast, stage- and age-specific sensitivity of digital mammography, breast cancer background incidence, stage- and age-specific mean duration of preclinical screen-detectable breast cancer and progression and regression of rate of DCIS were recalibrated.[2] This was done using data from the Dutch breast cancer screening programme on interval cancers (2004-2011), screen-detected cancers (2004-2013), and stage distribution at detection and data from the Netherlands Comprehensive Cancer Organisation (IKNL) on age-specific breast cancer incidence between 1975 and 2013. These calibrations led to model predictions that complied with Dutch breast cancer and breast cancer screening data and trends. Furthermore, the probabilities of receiving adjuvant treatment (no adjuvant treatment, hormonal therapy, chemo therapy, or combination therapy) were updated using data from IKNL over the years 2004-2013.[3]

Stage specific and age specific cure and survival rates after screen-detection were based on the Swedish randomised controlled trials.[4-7] Survival rates were also specified by lymph node status. The parameters were based on Dutch population data from Statistics Netherlands and IKNL complemented with data from meta-analyses from EBCTCG.[3,8,9]

Cost-effectiveness analyses

Diagnostic and treatment costs were specified per tumour stage. Data on costs and utilities were based on Geuzinge et al. and indexed to 2018 (Appendix Table 1).[10] Additionally, costs on biopsies were combined (€293.22) and costs of screening mammograms (€68.97) were updated based on the Dutch breast cancer screening monitor 2017-2018.[11] Furthermore, the costs of the last year of life before a breast cancer death compared to an other-cause death were updated with calculations based on data from Polder et al and Bakx et al., indexed to 2018 (€12,367.88, see appendix table 1).[12,13] QALYs were calculated by applying utility decrements on the average utility in Dutch women (0.858).[14] Utility decrements were used for screening participation (0.006), referral (0.105), life years of breast cancer treatment (stage specific), and cause of death (breast cancer or other causes).

FP findings were calculated using screen-detected cancers from the model output and the positive predicted value (PPV) of recall. PPVs were specified by age (<50 and ≥50) and screening interval. Biennial screening PPVs used were 12% for women <50, and 28% for women ≥50.[15-17] Ratios of the PPVs for annual and triennial screening were calculated based on findings in the U.S. Norway, and Spain.[18] Ratios for the PPVs for quadrennial screening were extrapolated based on the ratios for annual and triennial screening. These ratios were used to estimate PPVs for annual, triennial and biennial screening in the Netherlands. This

resulted in PPVs of 10% (<50) and 24% (≥50) for annual screening, 13% (<50) and 31% (≥50) for triennial screening, and 15% (<50) and 35% (≥50) for quadrennial screening.[2]

Appendix table 1

Appendix table 1 Price and utility parameters

Unit prices		
Procedure	**Price* (€)**	**Source**
Screening invitation	2	Sankatsing et al.[19]
Mammography (in screening setting)	68.97	IKNL monitor[11]
Mammography (in hospital setting)	91.97	Geuzinge et al.[10]
MRI	272	Geuzinge et al.[10]
Palpation	72.57	Geuzinge et al.[10]
Ultrasound	115.23	Geuzinge et al.[10]
FNA	293.22	Erasmus MC; CZ tariff tool[20]
Biopsy	293.22	Erasmus MC; CZ tariff tool[20]
GP consultation	17.69	Geuzinge et al.[10]
GP consultation (telephone)	34.34	Geuzinge et al.[10]
Treatment costs according to T-stage		
DCIS	5520	Geuzinge et al.[10]
T1a, N-	6376	Geuzinge et al.[10]
T1a, N+	6617	Geuzinge et al.[10]
T1b, N-	7441	Geuzinge et al.[10]
T1b, N+	10110	Geuzinge et al.[10]
T1c, N-	9073	Geuzinge et al.[10]
T1c, N+	9901	Geuzinge et al.[10]
T2+, N-	8480	Geuzinge et al.[10]
T2+, N-	8448	Geuzinge et al.[10]
Palliative therapy (last year of life) of breast cancer patients compared to palliative care for other causes of death	12,367.88	Calculations based on Polder et al. and Bakx et al.[12,13]
Health state	**Utility and duration**	**Source**
No breast cancer	0.858	Versteegh et al.[14]
Undergoing screening	0.006 (disutility) for 1 week	De Haes et al.[21]
Referral	0.105 (disutility) for 5 weeks	De Haes et al.[21]
DCIS/localised breast cancer	0.772 for 2 years	Stout et al.[22]
Regional breast cancer	0.644 for 2 years	Stout et al.[22]
Metastasis	0.515 until death	Stout et al.[22]
Death	0	

*All prices were indexed to 2018 using consumer price indices.

Appendix table 2

Appendix table 2 Age-specific participation rates

Age	Participation rate (%)	Source
40	69.66	Linear extrapolation based on age 50-65
41	70.04	Linear extrapolation based on age 50-65
42	70.42	Linear extrapolation based on age 50-65
43	70.80	Linear extrapolation based on age 50-65
44	71.18	Linear extrapolation based on age 50-65
45	71.56	Linear extrapolation based on age 50-65
46	71.94	Linear extrapolation based on age 50-65
47	72.32	Linear extrapolation based on age 50-65
48	72.71	Linear extrapolation based on age 50-65
49	73.09	Linear extrapolation based on age 50-65
50	73.46	Dutch participation data from April 2017 till April 2019
51	74.09	Dutch participation data from April 2017 till April 2019
52	74.25	Dutch participation data from April 2017 till April 2019
53	74.63	Dutch participation data from April 2017 till April 2019
54	74.69	Dutch participation data from April 2017 till April 2019
55	75.02	Dutch participation data from April 2017 till April 2019
56	75.87	Dutch participation data from April 2017 till April 2019
57	75.97	Dutch participation data from April 2017 till April 2019
58	77.07	Dutch participation data from April 2017 till April 2019
59	77.02	Dutch participation data from April 2017 till April 2019
60	76.94	Dutch participation data from April 2017 till April 2019
61	77.53	Dutch participation data from April 2017 till April 2019
62	78.29	Dutch participation data from April 2017 till April 2019
63	78.54	Dutch participation data from April 2017 till April 2019
64	78.83	Dutch participation data from April 2017 till April 2019
65	79.03	Dutch participation data from April 2017 till April 2019
66	79.00	Dutch participation data from April 2017 till April 2019
67	78.80	Dutch participation data from April 2017 till April 2019
68	78.95	Dutch participation data from April 2017 till April 2019
69	78.45	Dutch participation data from April 2017 till April 2019
70	77.93	Dutch participation data from April 2017 till April 2019
71	77.61	Dutch participation data from April 2017 till April 2019
72	76.09	Dutch participation data from April 2017 till April 2019
73	74.62	Dutch participation data from April 2017 till April 2019
74	73.24	Dutch participation data from April 2017 till April 2019
75	71.10	Dutch participation data from April 2017 till April 2019
76	69.78	Linear extrapolation based on age 71-75
77	68.19	Linear extrapolation based on age 71-75
78	66.60	Linear extrapolation based on age 71-75
79	65.02	Linear extrapolation based on age 71-75
80	63.43	Linear extrapolation based on age 71-75
81	61.84	Linear extrapolation based on age 71-75
82	60.26	Linear extrapolation based on age 71-75
83	58.67	Linear extrapolation based on age 71-75
84	57.08	Linear extrapolation based on age 71-75

Appendix table 3

Appendix table 3 Averages of recent treatment estimates by expert opinion. Stratified by mode of detection, tumour stage at diagnosis and age categories.

Screen detected breast cancers									
	DCIS	**T1AN-**	**T1AN+**	**T1BN-**	**T1BN+**	**T1CN-**	**T1CN+**	**T2+N-**	**T2+N+**
	% of patients receiving this treatment								
Age 35									
No adjuvant treatment	100.0%	100.0%	13.4%	75.9%	10.1%	16.2%	8.8%	0.7%	0.8%
Only hormonal treatment	0.0%	0.0%	5.1%	0.2%	1.0%	1.2%	0.7%	0.2%	0.4%
Only chemo therapy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Combination therapy	0.0%	0.0%	81.5%	23.9%	88.9%	82.6%	90.5%	99.1%	98.8%
Age 60									
No adjuvant treatment	100.0%	99.0%	6.7%	77.6%	10.6%	15.8%	10.1%	1.0%	1.1%
Only hormonal treatment	0.0%	1.0%	66.4%	6.3%	27.5%	31.0%	21.0%	7.8%	12.2%
Only chemo therapy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Combination therapy	0.0%	0.0%	26.9%	16.2%	61.9%	53.2%	68.9%	91.3%	86.7%
Age 75									
No adjuvant treatment	100.0%	88.7%	0.8%	49.0%	2.9%	3.8%	3.6%	1.0%	0.7%
Only hormonal treatment	0.0%	11.3%	99.1%	50.7%	96.6%	95.8%	95.7%	96.4%	97.7%
Only chemo therapy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Combination therapy	0.0%	0.0%	0.1%	0.3%	0.5%	0.4%	0.7%	2.6%	1.6%
Clinically detected breast cancers									
Age 35									
No adjuvant treatment	100.0%	85.2%	4.7%	42.1%	9.0%	3.0%	0.8%	0.4%	0.0%
Only hormonal treatment	0.0%	0.2%	0.2%	0.2%	0.8%	1.4%	0.2%	0.4%	0.1%
Only chemo therapy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Combination therapy	0.0%	14.6%	95.1%	57.7%	90.2%	95.6%	99.0%	99.2%	99.9%
Age 60									
No adjuvant treatment	100.0%	85.6%	6.5%	50.0%	10.1%	2.9%	1.1%	0.5%	0.0%
Only hormonal treatment	0.0%	4.7%	6.7%	4.7%	22.9%	35.8%	6.4%	14.5%	4.0%
Only chemo therapy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Combination therapy	0.0%	9.7%	86.8%	45.3%	66.9%	61.4%	92.5%	85.0%	96.0%
Age 75									
No adjuvant treatment	100.0%	58.6%	6.9%	44.8%	3.3%	0.6%	1.3%	0.3%	0.1%
Only hormonal treatment	0.0%	41.2%	90.3%	54.0%	96.0%	99.0%	95.5%	98.4%	94.6%
Only chemo therapy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Combination therapy	0.0%	0.2%	2.7%	1.2%	0.6%	0.4%	3.2%	1.3%	5.3%

Appendix table 4

Appendix table 4 Discounted model estimates of the number of life years gained (LYG) and additional costs (€) per 1,000 women compared to no screening with percentage change compared to the current strategy (B50-74). The table includes the current strategy and strategies on the efficiency frontier with corresponding ICERs.

Strategy	LYG		Additional costs (€)		ICER
Biennial 50-74	54.8	-	374,763	-	Dominated
Quadrennial 60-64	12.9	-76.5%	53,050	-85.8%	4,112
Quadrennial 56-64	20.8	-62.0%	87,100	-76.8%	4,310
Quadrennial 52-64	29.5	-46.2%	126,875	-66.1%	4,572
Quadrennial 50-66	35.2	-35.8%	161,450	-56.9%	6,066
Quadrennial 50-70	38.2	-30.3%	182,304	-51.4%	6,951
Quadrennial 49-69	39.4	-28.1%	191,039	-49.0%	7,279
Quadrennial 48-68	40.6	-25.9%	199,939	-46.6%	7,416
Quadrennial 47-71	44.3	-19.2%	228,179	-39.1%	7,633
Triennial 47-71	51.4	-6.2%	294,724	-21.4%	9,372
Triennial 46-70	52.8	-3.6%	307,927	-17.8%	9,431
Triennial 44-71	57.3	4.6%	354,556	-5.4%	10,362
Triennial 44-74	58.8	7.3%	372,241	-0.7%	11,790
Triennial 43-73	60.1	9.7%	388,503	3.7%	12,510
Triennial 42-72	61.4	12.0%	405,322	8.2%	12,938
Biennial 43-73	73.1	33.4%	565,623	50.9%	13,701
Biennial 42-74	75.7	38.1%	606,977	62.0%	15,906
Biennial 41-75	78.1	42.5%	649,316	73.3%	17,641
Biennial 40-74	79.6	45.3%	676,927	80.6%	18,407
Biennial 40-76	80.4	46.7%	692,550	84.8%	19,528
Biennial 40-78	80.9	47.6%	706,655	88.6%	28,210
Annual 40-75	102.9	87.8%	1,334,950	256.2%	28,559
Annual 40-76	103.4	88.7%	1,349,662	260.1%	29,423
Annual 40-78	104.1	90.0%	1,376,779	267.4%	38,739
Annual 40-81	104.7	91.1%	1,411,796	276.7%	58,362
Annual 40-84	105.0	91.6%	1,439,916	284.2%	93,733

* The strategy with a light grey background is not on the efficiency frontier, but included because it is the current strategy. The strategy with a dark grey background is the optimal strategy based on a WTP threshold of €20,000 per QALY gained. The other strategies with a grey background are candidate strategies based on more favourable QALYs and costs compared to the current strategy.

Appendix page 7

Sensitivity analyses

Taking into account age-specific attendance rates in all modelled screening strategies decreased the number of breast cancer deaths averted, number of overdiagnoses, number of false positives, amount of QALYs gained and additional costs (Table 3). This also slightly changed which strategies were present on the efficiency frontier and the accompanying ICERs.

For the biennial 40-76 strategy, the number of breast cancer deaths averted deceased by 19.7%, the number of overdiagnoses decreased by 19.2%, the number of false positives decreased by 22.0%, the amount of QALYs gained decreased by 20.4%, and the additional costs decreased by 23.8% compared to the base case analyses. Because the decrease in additional costs is larger than the decrease in QALYs gained, the ICERs also decreased. This led to strategy biennial 40-76 no longer being the first strategy under the WTP threshold of €20,000 per QALY. This became annual screening for the ages 42 till 73.

The triennial 44-71 and triennial 44-74 strategies were not on the efficiency frontier of these sensitivity analyses. The strategies with similar additional costs and more QALYs gained or similar QALYs gained and less costs in this analyses were biennial 47-71 and triennial 45-72.

When assumptions on current adjuvant treatment use were used, the number of breast cancer deaths averted, number of overdiagnoses, number of false positives, and amount of QALYs gained were slightly lower (Table 4). On the other hand, the amount of additional costs slightly increased. In addition, the strategies which were present on the efficiency frontier and the accompanying ICERs slightly changed compared to the base case analyses.

For biennial 40-76 screening, the number of breast cancer deaths averted deceased by 1.5%, the number of overdiagnoses decreased by 1.4%, and the number of false positives decreased by 0.6% compared to the base case analyses. The amount of QALYs gained did not change, whereas the additional costs increased by 2.1%.

The triennial 44-71 and triennial 44-74 strategies were not on the efficiency frontier of these sensitivity analyses. The strategy with less additional costs and more QALYs gained was triennial 45-72.

Appendix table 5

Appendix table 5 Discounted model estimates for sensitivity analyses using alternative assumptions on current adjuvant treatment use on the number of breast cancer (BC) deaths averted, overdiagnoses, QALYs gained, and additional costs (€) per 1,000 women compared to no screening with percentage change compared to the current strategy (B50-74). The table includes the current strategy and strategies on the efficiency frontier with corresponding ICERs.

Strategy	BC deaths averted		Over-diagnoses		False positives		QALYs gained		Additional costs (€)		ICER
Biennial 50-74	5.0	-	5.8	-	89	-	62.7	-	383,034	-	Dominated
Quadrennial 60-64	1.3	-75%	1.6	-72%	18	-80%	14.5	-77%	54,129	-86%	3,732
Quadrennial 56-64	1.9	-62%	2.2	-62%	25	-72%	23.7	-62%	88,823	-77%	3,763
Quadrennial 52-64	2.5	-50%	2.7	-54%	32	-64%	33.5	-47%	129,547	-66%	4,158
Quadrennial 51-67	3.0	-40%	3.3	-43%	38	-57%	39.0	-38%	158,542	-59%	5,265
Quadrennial 50-70	3.4	-32%	3.9	-33%	44	-51%	43.4	-31%	186,294	-51%	6,366
Quadrennial 48-68	3.4	-31%	3.7	-36%	57	-36%	46.1	-26%	204,092	-47%	6,485
Quadrennial 48-72	3.8	-24%	4.4	-25%	63	-30%	48.8	-22%	223,936	-42%	7,328
Triennial 48-69	4.1	-18%	4.4	-24%	77	-13%	54.7	-13%	269,588	-30%	7,752
Triennial 48-72	4.4	-12%	4.9	-15%	83	-7%	57.0	-9%	289,087	-25%	8,518
Triennial 45-72	4.7	-5%	5.2	-10%	99	11%	63.5	1%	347,909	-9%	9,108
Triennial 43-73	5.0	1%	5.6	-4%	114	28%	67.9	8%	397,785	4%	11,364
Biennial 44-72	5.8	16%	6.2	6%	137	54%	79.3	26%	536,399	40%	12,103
Biennial 43-73	6.0	21%	6.4	11%	151	70%	82.6	32%	578,591	51%	12,781
Biennial 42-74	6.2	25%	6.7	16%	153	72%	85.4	36%	619,847	62%	14,986
Biennial 40-74	6.4	29%	6.9	19%	163	83%	89.4	43%	691,263	80%	17,655
Biennial 40-76	6.5	31%	7.2	25%	167	87%	90.2	44%	707,331	85%	19,418
Biennial 40-78	6.6	34%	7.6	30%	170	91%	90.8	45%	721,858	88%	24,382
Annual 41-75	8.0	62%	8.4	45%	253	185%	112.8	80%	1,292,534	237%	25,947
Annual 40-75	8.2	65%	8.5	47%	262	194%	115.6	84%	1,364,127	256%	26,071
Annual 40-76	8.3	66%	8.7	50%	264	197%	116.1	85%	1,379,303	260%	29,868
Annual 40-77	8.3	68%	8.9	53%	267	200%	116.5	86%	1,393,641	264%	35,235
Annual 40-79	8.4	70%	9.3	60%	271	204%	117.1	87%	1,420,068	271%	46,054
Annual 40-80	8.5	71%	9.5	63%	273	207%	117.2	87%	1,432,175	274%	67,061
Annual 40-82	8.6	72%	9.8	69%	276	210%	117.5	87%	1,454,042	280%	89,147
Annual 40-84	8.6	73%	10.1	74%	279	213%	117.6	88%	1,472,859	285%	141,295

* The strategy with a light grey background is not on the efficiency frontier, but included because it is the current strategy. The strategy with a dark grey background is the optimal strategy based on a WTP threshold of €20,000 per QALY gained. The other strategies with a grey background are candidate strategies based on more favourable QALYs and costs compared to the current strategy.

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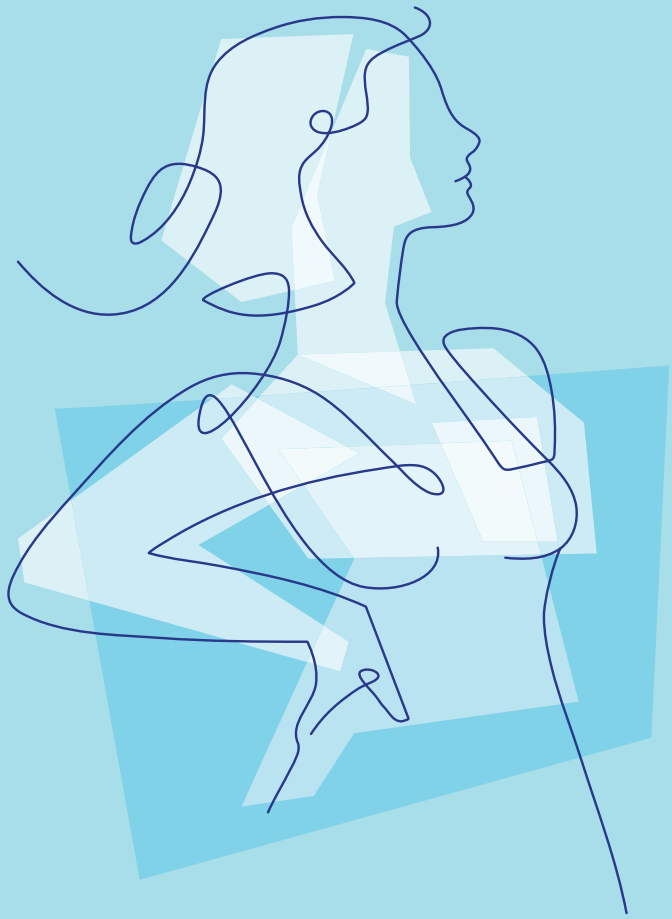
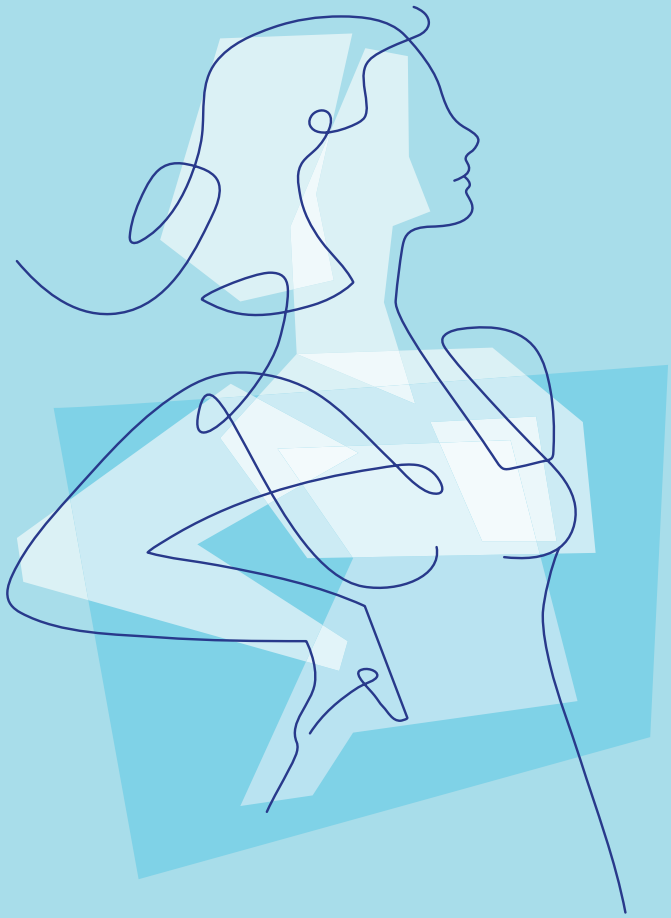


Part 2

Perspectives of the women



7

Effects of a leaflet on Breast Cancer Screening Knowledge, Explicit Attitudes, and Implicit Associations

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ABSTRACT

Objective

To assess the effect of an information leaflet on knowledge, explicit attitudes, implicit associations, and attendance for breast cancer screening.

Methods

Dutch women (aged 49-75 years) were approached three months before their breast cancer screening invitation. After providing informed consent, participants were randomised to receiving the information leaflet (intervention condition) or not (control condition). Screening knowledge, explicit attitudes, and implicit associations were assessed through web-based questionnaires, at baseline and two weeks later. Actual screening attendance data were collected.

Results

In total, 988 women completed both questionnaires. Participants in the leaflet condition scored higher on knowledge (9.9 versus 9.6, $p<0.001$, scale 0-11), and more often had positive explicit attitudes (97% versus 95%, $p=0.03$), than those in the control condition. This contrast was bigger among first-time invitees. Implicit associations were not correlated with explicit attitudes or attendance. Explicit attitudes were moderately correlated with attendance ($r=.30$, $p<0.001$).

Conclusion

The information leaflet led to more knowledge and more positive explicit attitudes. Implicit associations towards breast cancer screening were not correlated with attendance.

Practice implications

Encouragement to learn about the screening programme can increase levels of knowledge of invitees and therefore support their decision-making about participation. This might be especially relevant for first-time invitees.

INTRODUCTION

Individual behaviour is shaped by attitudes.[1] Two different types of attitudes can be distinguished: explicit attitudes and implicit associations.[2] Explicit attitudes are deliberate and are present at the conscious level.[1,2] People are conscious of their explicit attitudes and are able to self-report them. In contrast to explicit attitudes, implicit associations can influence and guide behaviour without people's conscious awareness, they can result in spontaneous or automatic behaviour.[1,2] Explicit attitudes and implicit associations can be contradictory.[2] It has been shown that implicit associations can affect consumer behaviour and decision-making[3-5], but little is known to what extent they affect medical decision-making about, for instance, cancer screening.

Participation in population-based breast cancer screening programmes is voluntary and usually free-of-charge. In the Netherlands, eligible women (ages 50-75) receive a personal invitation each screening round accompanied by an information leaflet about the procedure, and harms and benefits of breast cancer screening. The information is aimed at enabling women to make an informed choice about whether or not to participate in the screening.[6,7] However, it is unclear to what extent the current information leaflet (2018) contributes to the knowledge of women, and whether it effects explicit attitudes, implicit associations, and attendance.

Attendance rates of breast cancer screening programmes in the Netherlands, England, Finland, and the USA slightly decreased over the past years (e.g. the Netherlands: from 82.4% in 2007 to 76.6% in 2018).[8-12] To better understand this decrease and the way women decide to participate in breast cancer screening or not, more insight into knowledge, explicit attitudes, and implicit associations is useful. It is currently unknown if and to what extent attendance to the breast cancer screening programme is associated with explicit attitudes or implicit association.

The aim of this study was to examine the influence of an information leaflet on the level of decision-relevant knowledge about breast cancer screening, explicit attitudes and screening attendance among women invited for breast cancer screening. This study also aimed to investigate the association between explicit attitudes as well as implicit associations towards the Dutch breast cancer screening programme and attendance.

METHODS

Population

Women, aged 49-75, living in the South West screening region of the Netherlands, who were due to be invited for breast cancer screening were approached to participate in this study by a joint letter from the local screening organisation 'Bevolkingsonderzoek Zuid-West' and Erasmus MC. The letters were sent in November and December 2018 and included study information, an invitation to participate, and an informed consent form. Women who were registered at the screening organisation as 'not willing to participate in research' were not approached to participate in this study. During five to 10 years following a breast cancer diagnosis women are not invited for the regular screening program, and therefore this group of women was not included in our study. Having no email address or internet access was an exclusion criterion.

Sample size calculation

Sample size calculation indicated that 834 women needed to participate to be able to show an effect in response time with 80% power and statistical significance of 0.05. Based on the participation rate in a previous study evaluating the screening programme, we expected a participation rate of about 30% among screening attenders and about 10% among non-attenders.[6]

Potential participants were selected by the regional screening organisation (Bevolkingsonderzoek Zuid-West) based on postal code. To reach a representable population of participating and non-participating women, women who had declined participation in previous screening rounds were oversampled. In total, 5,568 women were invited, of which 1,211 (22%) women had not participated in previous screening rounds, 3,817 (68%) women had participated in previous screening rounds, and 540 (10%) women were to receive their first screening invitation.[12]

Design

Women who provided consent and their e-mail address were randomised to the intervention condition (leaflet) or the control condition (no leaflet) by computer-generated random numbers. Subsequently, a link to a web-based questionnaire was sent to the participants by e-mail. The questionnaire started with a short introduction to the Dutch national breast cancer screening programme and contained questions regarding intention to participate, explicit attitudes, knowledge about the screening programme, reasons to participate or not, and demographics. A priming task was included to assess implicit associations. Two weeks after completing their first questionnaire, participants in the intervention group were asked to read an online information leaflet (see below).

Participants in the control condition did not receive this leaflet. Then, all participants were asked to complete the second questionnaire (see figure 1). Subsequently, following the regular invitation schedule, all respondents received an invitation to participate in the breast cancer screening programme and the information leaflet.

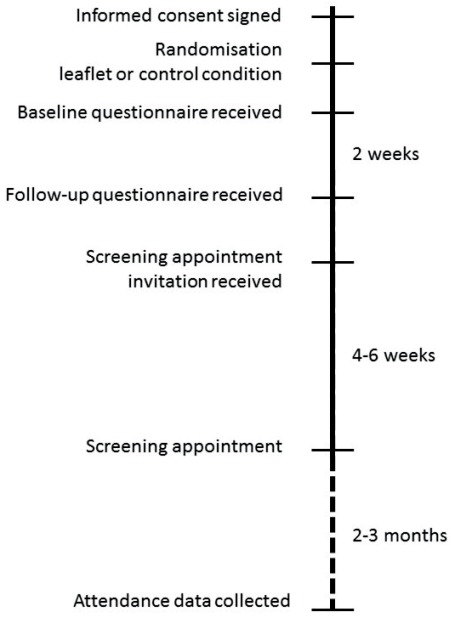

Figure 1 data collection timeline

Since it is not always feasible to assess actual participation, previous studies concerning informed choice, often assessed intention to participate as a proxy for actual participation. Although strongly correlated, intention to participate in screening is not necessarily similar to actual screening attendance and can be considered to be more influenced by explicit attitudes.[13,14] Therefore, this study will study the effects of both intention and actual attendance. Conditional on provided consent, attendance data for this screening round were provided by the screening organisation. Collection of attendance data took place two to three months after the planned screening appointment.

Intervention

Women in the intervention group were provided the official breast cancer screening information leaflet from the Dutch National Institute for Public Health and the Environment (RIVM). The leaflet was developed based on the opinion of experts who recommended "[using] simple texts without numerical values to present information on difficult topics as false positives and over-diagnosis".[6] Therefore, the leaflet was designed to increase the level of gist knowledge, i.e. "the ability to identify the essential points of the information presented", rather than verbatim knowledge, i.e. "the ability to correctly read numbers from graphs".[15]

The January 2018 version (appendix figure 1) contains information about the screening invitation, the screening process, possible screening outcomes, and the benefits and harms of screening. Unlike most official information leaflets, potential harms such as overdiagnosis, overtreatment, false-negatives, and interval cancers were described explicitly.[16]

Content of the questionnaires

The baseline questionnaire included demographic questions about screening history, living situation, educational level, employment status, and home language of the respondent.

Gist knowledge about the breast cancer screening programme was determined using 11 statements (based on expert consultations); response options were 'true', 'false', or 'I don't know'.[6] In the absence of an agreed external criterion to define 'sufficient' knowledge, it was operationalised as a minimum of eight correct answers.[6,17-19] Participants' explicit attitudes towards breast cancer screening were measured through an attitudes scale derived from the multidimensional informed choice measure of Marteau et al..[20] It contained six cognitive items regarding the breast cancer screening programme, such as 'I think participation in the breast cancer screening programme within three months for me would be useless/useful'. Participants responded on 7-point-likert scales. In accordance with guidelines, missing items on the attitudes scale were imputed by individuals' mean score, if at least 50% of the items had been completed.[21] The results were transformed to a 0-100 scale and categorised as negative (<50) or positive (≥50) attitudes.

Participants were asked how likely they were to participate in the breast cancer screening programme if they would receive an invitation within the coming three months. The answers were given on a 7-point-likert scale. Scores 1 and 2 were classified as a negative intention, 3 to 5 as a neutral intention, and 6 and 7 as a positive intention.

Following the model of Marteau et al., a woman was considered to have made an informed choice when she had sufficient knowledge about the breast cancer screening program, a positive attitude towards participating in this program, and participated in the programme, or when she had sufficient knowledge, a negative attitude and did not participate in the programme.[20]

To assess participants' implicit associations, a priming task was used. Priming tasks are widely used in social cognition research, and were originally developed to assess implicit associations towards social groups or activities.[3-5,22] During priming tasks, people are shown primes (pictures or words) of a topic of interest followed by target words. The target words used are distinctively positive or negative. The participants are asked to respond to the target word and indicate if it was positive or negative. The task relies on the assumption that the prime automatically activates an evaluation, and that if primes and target words are strongly associated in the participant's mind, the participant will react more quickly.[23] Therefore, the response time to the task was assumed to be shortest when the participant strongly associated the prime with the presented target.[22]

In the priming task, a screening, neutral and non-word prime were used. The prime words chosen had to be short, simple and representative. For the screening prime, "Röntgenfoto" (X-ray) was found to be too long and difficult for quick reading and less typical for breast cancer screening. Therefore, we opted for "Borstfoto's" (breast X-rays/pictures) which was a more simple and clear referral to breast cancer screening. Since this prime was crucial, we checked with healthcare providers, a patient organisation and the collaborating local screening organisation (BOZW) whether they agreed. The neutral prime, "Brievenbus" (mailbox), was chosen because of its neutral meaning and because it had the same amount of syllables as the screening prime. The non-word prime was a random order of consonants at about the same length as the other primes ("Fjnmpklzv").

Each of the primes was shown on the computer screen, followed after a 100ms interval by a target word. The target words could be positive or negative (for example 'good' or 'bad'). The respondents were asked to state as quickly and accurately as possible whether the shown target was positive or negative by pressing a specific key on their keyboard (i.e. the keys "L" and "A", respectively). The complete priming task consisted of 24 combinations of primes and targets, in which all combinations of the three primes and eight targets were presented once, in a random order. Due to misconceptions regarding one of the targets (double meaning in Dutch) the response times for this target were excluded for analyses.

Response times considered to be too fast (quicker than 300 milliseconds (ms)) or too slow (slower than 3000 ms) were excluded.[24] Also, response times were excluded in case of incorrect responses, e.g. in case the positive key "L" was pressed after the negative word "bad". Implicit associations were then calculated per prime by subtracting the average response times for the negative targets from the average response times for the positive targets.

Statistical analyses

T-tests and chi-square tests were performed to test for differences between the two randomised groups in attendance, explicit attitudes, implicit associations, knowledge, and informed choice. Subsequently, Pearson's, Phi, and Cramer's V correlations were measured between implicit associations, explicit attitudes, intention to participate, attendance, knowledge about breast cancer screening, level of education, previous invitation for breast cancer screening, previous attendance in breast cancer screening, and previous referrals based on breast cancer screening results.

Subgroup analyses were performed for participants who were invited for the national breast cancer screening programme for the first time. These first-time invitees were identified based on self-reporting to not have had a previous invitation. Differences in response times between left and right handed respondents were also tested.

Repeated measures ANOVAs were performed to test for differences in response time between the primes and targets in the priming task. The interaction term ("prime*target") was also included. Subsequently, a repeated measures ANCOVA was performed taking into account the covariates that were significant in the correlations analyses.

All analyses were performed in IBM SPSS Statistics, version 24 and statistical significance was set at $\alpha = 0.05$.

RESULTS

Background characteristics

In total, 5,568 study invitations were sent out and 1,372 informed consent forms were received (response rate 25%) (figure 2). Of these, 25 were received too late and 35 were invalid. The 1,312 included participants were randomised to the leaflet (n=703, 54%) and the control condition (n=609, 46%).

Thirty-five women (2.7%) were excluded due to unknown or invalid email addresses, and 28 (2.1%) women withdrew from participation after being sent the first questionnaire due to lack of time or technical issues. In total, 1073 participants (83%) completed the first questionnaire. After being sent the second questionnaire, another six participants (<1%) withdrew from participation. In total, 988 participants (92%) completed the second questionnaire.

Data-analyses included 988 participants; 531 in the leaflet condition and 457 in the control condition. Of these, 904 (92%) also gave consent to collect attendance data from the screening organisation. Baseline characteristics of the two randomised groups were similar (Table 1). Participants were on average 60 years of age ranging from 49 to 75 in both conditions.

Informed choice

At baseline, the average knowledge score was 9.3 (on a scale of 0 to 11). At follow-up, a difference was seen between the leaflet and control condition (9.9 versus 9.6, respectively, $p<0.001$). This resulted in 94% and 91% of participants having sufficient knowledge in the two respective groups (p=0.09). At baseline, 96% had positive explicit attitudes, at follow-up these percentages were 97% in the leaflet condition and 95% in the control condition (p=0.03). No differences in screening attendance were found between the leaflet and control condition (90% versus 88%, respectively, p=0.46).

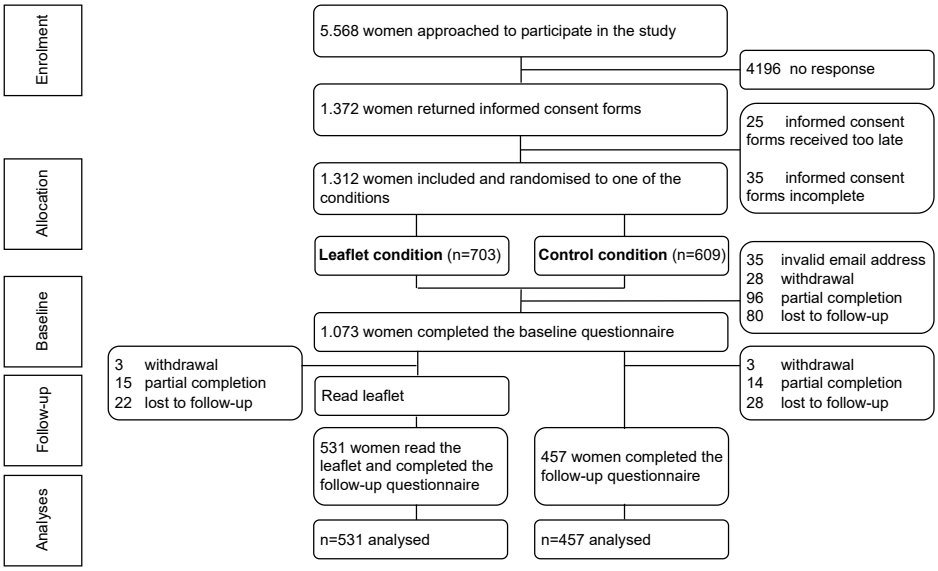

Figure 2 Flowchart

In total, 718 women (80%) made an informed choice. Of them, 701 made the decision to participate in screening and 17 not to participate, see Figure 3A. About half of the uninformed choices were due to insufficient knowledge. Differences in informed choice between the two conditions were not significant (i.e. in the leaflet condition 84% made the informed choice to participate and 2% not to participate compared to 78% and 3% in the control condition, p=0.07).

Subgroup analyses of first-time invitees

At baseline, 80% of first-time invitees had sufficient decision-relevant knowledge versus 89% of women in the total population (Appendix Table A1). After reading the leaflet, 93% of first-time invitees reported sufficient knowledge versus 77% of first-time invitees in the control condition. The attendance rate was 83% among the first-time invitees versus 89% in the total population. The rate of women with positive explicit attitudes was similar for first-time invitees and the total population (97% versus 96%).

The lower level of knowledge and the lower attendance resulted in a lower proportion of first-time invitees who made an informed choice (66%). Again about half of the uninformed choices were due to insufficient knowledge (Figure 3B).

Implicit associations

At baseline, 505 women completed the priming task. However, 26 of them withdrew, only partially completed the second questionnaire, or were lost to follow-up. Therefore, baseline

Table 1 Participant characteristics (n=988)

	Leaflet condition (n=531)	Control condition (n=457)	p-value
Age			
Mean (SD)	60.1 (6.7)	59.9 (6.9)	0.15
Range	48.5 - 75.0	49.0 - 74.9	
Missing	0	0	
Educational level (n,%)			
High	146 (28)	123 (27)	0.44
Middle	287 (55)	239 (53)	
Low	87 (17)	90 (20)	
Missing	11	5	
Language spoken at home (n,%)			
Dutch	454 (96)	407 (98)	0.13
Dutch and other	8 (2)	2 (1)	
Other	10 (2)	5 (1)	
Missing	59	43	
Living situation (n,%)			
With partner	441 (84)	366 (80)	0.21
Not with partner	87 (17)	89 (20)	
Missing	3	2	
Working status (n,%)			
Paid work	293 (60)	250 (59)	0.85
No paid work	64 (13)	53 (13)	
Retired	129 (27)	119 (28)	
Missing	45	35	
Previously invited to participate in breast cancer screening (n, %)			
Yes	464 (88)	397 (87)	0.77
Do not remember	6 (1)	4 (1)	
No	58 (11)	56 (12)	
Missing	3	0	
Previously participated in breast cancer screening (n,% of invited)			
Yes	427 (93)	374 (94)	0.40
No	32 (7)	22 (6)	
Missing	5	1	
Previously referred for further diagnostics (n,% of participated)			
Yes	62 (15)	46 (12)	0.36
No	365 (86)	328 (88)	
Missing	0	0	

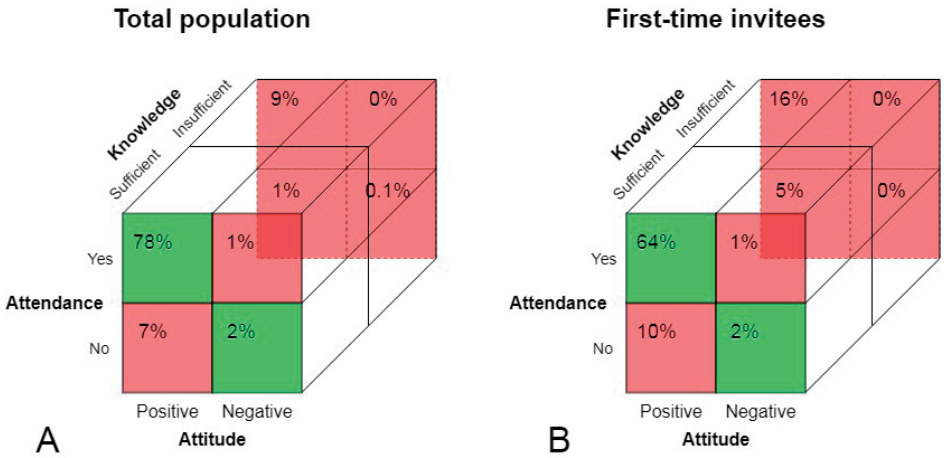

Figure 3 Classification of informed choice according to Marteau et al. (18). A) total baseline population B) subgroup baseline analyses of first-time invitees. Green: informed choice, Red: no informed choice
** Percentages are rounded off, so they may not add to 100%.*

priming task data of 479 (48% of 988) women were analysed. At follow-up, priming task data of 522 (53%) women were analysed (Table 2). Participants pressed the correct key (i.e. the key corresponding to the target) 87-89% of the time. No significant difference in accurate responses was seen between the conditions. On average, responses were a little quicker (i.e. response times were shorter) when positive or neutral targets followed the screening prime versus negative targets, resulting in a positive mean difference in response times (17.9 ms and 34.2 ms, respectively) at baseline. For the non-word prime, responses were on average slower for positive targets than for negative targets, resulting in a negative mean difference in response times (-26.7 ms). This trend was also seen for the leaflet condition at follow-up. In the control condition, average responses were slower for positive targets for all three primes. However, the standard deviations were large for all mean differences. No differences were seen between the two conditions. No differences were found in response times between left and right handed participants (results not shown).

No correlations were found between implicit associations and explicit attitudes or between implicit associations and intention to participate (Table 3). Also, no correlation was found between implicit associations and attendance (r=.05, p=0.33).

Explicit attitudes were found to be strongly correlated with intention to participate, and moderately with attendance (Table 3). Intention to participate was found to be moderately correlated with attendance. A moderate correlation was also found between attendance and previous participation. Intention and attendance were found not to be correlated with implicit associations.

Table 2 implicit associations, explicit attitudes, knowledge, intention to participate, attendance, and informed choice of breast cancer screening at baseline and follow-up, split for leaflet and control group.

	Baseline	**Follow-up**		
		Leaflet	**Control**	**P-value**
	n= 988	n= 531	n= 457	
Implicit associations	**n (%)**			
Participants completing the priming task	479 (48)	300 (57)	222 (49)	**<0.01**
	Mean difference in response time in milliseconds (SD)			
Screening prime & negative target minus screening prime & positive target	17.9 (431)	3.6 (432)	-2.7 (436)	0.99
Neutral prime & negative target minus neutral prime & positive target	34.2 (377)	24.9 (401)	-38.6 (367)	0.35
Non word prime & negative target minus non word prime & positive target	-26.7 (415)	-13.7 (434)	-28.8 (419)	0.59
	Mean % (SD)			
Accurate responses to target words	87 (18)	89 (17)	87 (18)	0.14
Explicit attitudes	**n (%)**			
Positive	945 (96)	516 (97)	432 (95)	**0.03**
Negative	41 (4)	14 (3)	24 (5)	
Missing	*2*	*1*	*1*	
Levels of knowledge (0-11)				
Mean (range)	9.3 (2 - 11)	9.9 (4 – 11)	9.6 (2 – 11)	**<0.001**
Sufficient knowledge (≥8) n (%)	869 (89)	486 (94)	409 (91)	0.09
Intention to participate	**n (%)**			
Positive	929 (94)	507 (96)	423 (93)	0.15
Neutral	33 (3)	15 (3)	21 (5)	
Negative	25 (3)	9 (2)	13 (3)	
Missing	*1*	*0*	*0*	
Participation	**n (%)**			
Participated	803 (89)	437 (90)	366 (88)	0.46
Did not participate	101 (11)	51 (11)	50 (12)	
Missing	*84*	*43*	*41*	
Informed choice	**n (%)**			
Yes, informed choice to participate in screening	701 (78)	403 (84)	321 (78)	0.07
Yes, informed choice not to participate in screening	17 (2)	8 (2)	11 (3)	
No, not an informed choice	186 (21)	71 (15)	82 (20)	
Missing	*84*	*49*	*43*	

Table 3 Correlations between intention, attendance, implicit associations and explicit attitudes regarding breast cancer screening and educational level, screening history, knowledge about the screening programme.

	Baseline, entire group (n=988)			
	Implicit associations	**Explicit attitude**	**Intention**	**Attendance**
Implicit associations, i.e. the difference in response time to [screening prime & negative target] versus [screening prime & positive target]	-	-.03 (p=0.83)	-.05 (p=0.31)	.05 (p=0.33)
Explicit attitude	-.03 (p=0.83)	-	**.64 (p<0.001)**	**.30 (p<0.001)**
Intention to participate	-.05 (p=0.31)	**.64 (p<0.001)**	-	**.42 (p<0.001)**
Attendance	.05 (p=0.33)	**.30 (p<0.001)**	**.42 (p<0.001)**	-
Knowledge	.08 (p=0.08)	-.03 (p=0.40)	.03 (p=0.35)	.03 (p=0.32)
Educational level	.01 (p=0.80)	**-.18 (p<0.001)**	**-.09 (p<0.01)**	.01 (P=0.95)
Previously invited to participate in breast cancer screening	.05 (p=0.30)	.00 (p=0.92)	-.02 (p=0.45)	**.07 (p=0.03)**
Previous participation in breast cancer screening	-.04 (p=0.43)	**.37 (p<0.001)**	**.59 (p<0.001)**	**.44 (p<0.001)**
Previously referred for further diagnostics	-.05 (p=0.39)	.00 (p=0.95)	-.01 (p=0.83)	**-.09 (p=0.02)**
	Follow-up, leaflet condition (n=531)			
	Implicit associations	**Explicit attitude**	**Intention**	**Attendance**
Implicit associations, i.e. the difference in response time to [screening prime & negative target] versus [screening prime & positive target]	-	.01 (p=0.90)	.01 (p=0.86)	-.05 (p=0.45)
Explicit attitude	.01 (p=0.90)	-	**.67 (p<0.001)**	**.30 (p<0.001)**
Intention to participate	.01 (p=0.86)	**.67 (p<0.001)**	-	**.40 (p<0.001)**
Attendance	-.05 (p=0.45)	**.30 (p<0.001)**	**.40 (p<0.001)**	**-**
Knowledge	.01 (p=0.94)	.06 (p=0.19)	.07 (p=0.10)	.07 (p=0.15)
Educational level	.10 (p=0.09)	**-.22 (p<0.001)**	**-.10 (p=0.02)**	.08 (p=0.20)
Previously invited to participate in breast cancer screening	-.01 (p=0.92)	-.02 (p=0.68)	-.07 (p=0.13)	.02 (p=0.62)
Previous participation in breast cancer screening	.05 (p=0.45)	**.39 (p<0.001)**	**.52 (p<0.001)**	**.47 (p<0.001)**
Previously referred for further diagnostics	.04 (p=0.60)	.03 (p=0.56)	.01 (p=0.82)	-.10 (p=0.05)

Table 3 Correlations between intention, attendance, implicit associations and explicit attitudes regarding breast cancer screening and educational level, screening history, knowledge about the screening programme. (continued)

	Follow-up, control condition (n=457)			
	Implicit associations	**Explicit attitude**	**Intention**	**Attendance**
Implicit associations, i.e. the difference in response time to [screening prime & negative target] versus [screening prime & positive target]	-	.0 (p=0.92)	.09 (p=0.20)	.04 (p=0.61)
Explicit attitude	-.01 (p=0.92)	-	**.69 (p<0.001)**	**.33 (p<0.01)**
Intention to participate	.09 (p=0.20)	**.69 (p<0.001)**	-	**.47 (p<0.001)**
Attendance	.04 (p=0.61)	**.33 (p<0.001)**	**.47 (p<0.001)**	-
Knowledge	.04 (p=0.54)	.01 (p=0.83)	.07 (p=0.12)	.04 (p=0.46)
Educational level	-.08 (p=0.24)	**-.15 (p=0.001)**	**-.09 (p=0.05)**	.07 (p=0.41)
Previously invited to participate in breast cancer screening	.06 (p=0.42)	.05 (p=0.29)	.07 (p=0.17)	**.12 (p=0.02)**
Previous participation in breast cancer screening	.06 (p=0.47)	**.39 (p<0.001)**	**.56 (p<0.001)**	**.40 (p<0.001)**
Previously referred for further diagnostics	-.05 (p=0.57)	-.03 (p=0.61)	-.03 (p=0.64)	-.08 (p=0.16)

Table 4 Repeated measures analyses (ANOVA)

	F-test	**Degrees of freedom**	**p-value**	**Effect size**
	Baseline			
Prime	0.420	2; 402	0.66	0.002
Target	0.327	1; 403	0.57	0.001
Prime * target	2.078	2; 402	0.13	0.010
ANCOVA[1]				
Prime	0.469	2; 324	0.63	0.003
Target	1.982	1; 325	0.16	0.006
Prime * target	1.571	2; 324	0.21	0.010
	Follow-up			
Prime	0.086	2; 431	0.92	0.000
Target	0.761	1; 432	0.38	0.002
Prime * target	0.216	2; 431	0.81	0.001
Prime * condition	2.402	2; 431	0.09	0.011
ANCOVA[1]				
Prime	2.255	2; 358	0.11	0.012
Target	0.278	1; 359	0.60	0.001
Prime * target	1.080	2; 358	0.34	0.006
Prime * condition	2.835	2;358	0.06	0.016

[1] corrected for the variables educational level and previous participation in breast cancer screening

Repeated measures ANOVA did not show any significant prime effects, target effects or interaction effects for prime*target (Table 4). Thus there were no differences in average response times between the different primes, between the different targets, and between certain combinations of primes and targets. No significant difference was found for the interaction term prime*condition meaning that there were no differences in response times for the different primes between the leaflet and control condition.

DISCUSSION

Discussion

The results of our study show that women who were provided with the information leaflet reported better knowledge, and more often positive explicit attitudes. This contrast was larger among first-time invitees. Implicit associations were not associated with explicit attitudes towards breast cancer screening. Explicit attitude was found to be associated with attendance, while implicit associations were not.

In an earlier study on informed choice in the Dutch breast cancer screening programme a rate of 88% informed choices among first-time invitees was reported.[6] This finding was based on intention to participate rather than actual attendance, which may explain the difference with the 66% as found in the current study. The positive effect of the leaflet on knowledge and informed choice confirms the findings of two studies in Australia.[17,25] One study found that women who received a decision aid leaflet for breast cancer screening with evidence-based information about breast cancer mortality reduction, over-detection, and false positives in screening had more knowledge and more often made an informed choice than women who received a similar leaflet without information about over-detection.[25] The other study found that 40-year-old women who received an online decision aid regarding breast cancer screening were more knowledgeable and less likely to be uncertain about their intention to participate than women who did not receive the aid, although this study found no difference in informed choice between the two groups.[17] Both studies found a reduction in intention to participate in the screening when women received an extensive decision aid, however this was not the case in our study.[17,25] Our results showed that asking women explicitly to read the leaflet increased their level of knowledge, but did not deter them from participating in screening. The use of the official information leaflet as designed by the Dutch National Institute for Public health and the Environment (RIVM) is a strength of this study. This leaflet is already routinely provided to every woman invited for breast cancer screening in the Netherlands. No further implementation is needed to see the effects found, whereas, in other studies, new leaflets or decision-aids were developed within the study that may not be implemented by policy

makers.[25-27] Further research should be aimed at motivating women to read the leaflet, to increase its potential effect.

A meta-analyses of 126 studies found that correlations between implicit associations and explicit attitudes tended to be small and were even more reduced when they considered socially sensitive topics.[28] This study did not find a correlation between implicit associations and explicit attitude towards breast cancer screening. Possibly participants may have felt a pressure to give socially desired answers, which made the topic partly socially sensitive therefore the meta-analysis is in line with our findings. No correlation was found between implicit associations and intention to participate or attendance in breast cancer screening. This is similar to the results of Korfage et al., who found no correlation between implicit associations and intention to participate in cervical cancer screening.[14]

This study is unique in analysing informed choice in screening using actual attendance data. So far, studies used intention to participate as a proxy for actual attendance. The correlation found between intention to participate and attendance was only r=.42 ($p<0.001$). This means that there was an association between intention to participate and attendance, but that a number of participants had an intention that was deviating from their actual attendance. Therefore, we think it is a strength of this study that actual attendance data was used. A weakness of this study was that only about half of the participants completed the priming task. This reduced the power of the analyses and could have led to selection bias. Comparing demographics, the participants who completed the priming task were more often higher educated, less often retired, and more often first-time invitees than the participants who did not complete the priming task. No differences were seen in age, living conditions, and previous participation in the screening programme. Reasons why participants completed the questionnaire, but did not complete the priming task were not fully known, although some participants reported medical or technical difficulties. A limitation of this study is that it was not possible to address women who opted out from the breast cancer screening programme. Also the fact that 89% of the participants in this study attended the screening programme versus 76% in this specific region in the previous screening round, 96% reported a positive explicit attitude, 96% had a positive intention to participate, and 89% had sufficient knowledge at baseline indicates that study participants were probably more positive about breast cancer screening than the average population.[29] Still, the two randomised groups were comparable.

It is important that women have sufficient decision-relevant knowledge about the advantages and disadvantages of participating in breast cancer screening and are enabled to make an informed choice.[7] It could be argued that this is especially important when they make this decision for the first time, since future attendance had been shown to be

strongly related to attendance at the first screening round.[30] Our results indicate that the information leaflet increases the knowledge of women about the breast cancer screening programme. This effect was the largest in the subgroup of first-time invitees. Although most participants in this study had been invited for the screening programme multiple times before and therefore had received this (or a similar) information leaflet previously, this study still found an increase in knowledge after receiving the leaflet. Possibly not all women read the leaflet when they receive it with the invitation or they may have forgotten details over time. We expected that in the context of the study, participants were more likely to read the leaflet more intensively than when they received it with the screening appointment invitation. Therefore, the found effects on knowledge and explicit attitudes may be smaller in practice.

Practice Implications

The information leaflet can help increase knowledge about the screening programme and thereby increase the number of women making an informed choice. This is especially important for women who are invited for the first time, because their level of knowledge is lower.

We recommend to raise attention towards and interest in reading the official leaflet. This is important to keep women up-to-date about changes and insights concerning the screening programme. Next to that, new research can explore how information can best be provided. Different modes of delivering information to women can be studied, such as infographics or movies, as well as exploring the use of different distribution channels such as email, publishing in local newspapers, via social media, or via community groups. A barrier might be that women are invited for breast cancer screening biennially over a period of 24 years and are therefore potentially not interested in gathering information every time they are invited. Possibly, more personalised information can be offered to first-time invitees and previously invited participants.

Conclusion

In conclusion, providing an information leaflet to women invited for breast cancer screening led to slightly higher levels of knowledge, and more women with positive explicit attitudes, in particular amongst women who were invited for the first time. In first-time invitees baseline knowledge was less often sufficient, but the leaflet increased this. Intention to participate and attendance seem to be associated with explicit attitude, however, not with implicit associations.

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APPENDIX

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

National Programme for Breast Cancer Screening

Invitation

What is the national programme for breast cancer screening?

The national programme for breast cancer screening tries to detect breast cancer. All women in the Netherlands aged 50 to 75 will receive an invitation every two years to participate. If you take part, we will take X-rays of your breasts. This allows us to detect breast cancer even before you start noticing anything is wrong.

Why is there a screening programme?

One in seven women in the Netherlands will develop breast cancer. The screening programme is intended to detect breast cancer at the earliest possible moment. The sooner breast cancer is detected, the bigger the chance of successful treatment. It also means that in many cases, less radical treatment is required.

What is this brochure for?

This brochure discusses the national programme for breast cancer screening. It is up to you whether or not you participate. The information in the brochure will help you decide.

The screening programme is free
Participation in the screening programme is free of charge. You may require subsequent examination at the hospital. This follow-up examination is not part of the screening programme. These costs are covered by your health care insurance. You may be obliged to pay the costs, or a part of them, yourself. This depends on your excess amount and how much you have already used of this. Do you have any questions about this? If so, please contact your health care insurer.

What is breast cancer?

- The body consists of millions of cells. Changes in cells can cause the cells to grow too fast and damage the body. This is called cancer.
- There are different types of cancer. The most common type of cancer in women is breast cancer.
- In the beginning, breast cancer can develop without you even noticing anything.
- Breast cancer may grow slowly, but its spread can also be rapid. This varies per person.
- Women can die of breast cancer. If breast cancer is detected early on, there is a better chance of curing it.

More information about breast cancer
www.borstkanker.nl
www.kwf.nl

If you notice changes in your breast, please visit your GP
The screening programme is intended for women who do not have any symptoms. Do you have any of the following symptoms?
- A lump in your breast.
- An indentation or dimple in the skin of your breast.
- Thicker skin than normal in an area of your breast.
- Bloody discharge from your nipple.
- Changes in your nipple.
- Your breast feeling different.

In that case, do not wait for an invitation for the screening, but contact your GP.

The screening in five steps

1. The letter

This brochure was accompanied by a letter, with an appointment to have X-rays of your breast taken.

Please bring the letter and valid proof of identity (passport, ID card or driving license) to the appointment.
The appointment lasts about 20 minutes.

2. The screening centre

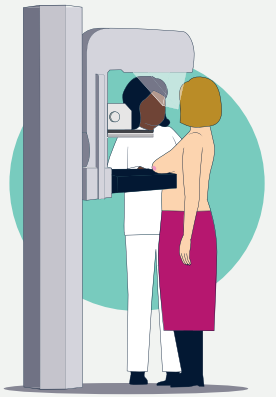
The examination takes place at a screening centre near you.
An employee will check your information.
You will then be asked to wait in the waiting area.

3. X-rays

Is it your turn? Please remove the top part of your clothing in the dressing room. We will inform you about the procedure. Do you have any scarring on your breasts? Or are your breasts highly sensitive? If you tell us about this, we can take this into account.

We will take two X-rays of each breast. In some cases, more X-rays are required. For each image, we will press your breast between two plates for a couple of seconds. This is necessary to produce a clear image, with as little radiation as possible.

This compression process may be painful, but it does not harm your breast. In some cases, it can cause bruising. Is the pressure too painful? Please inform our employee.



4. Have we succeeded in taking all images?

Once all images have been taken, you can get dressed again and go back to wait in the waiting area. We will check if the images show enough of the breasts, and if the images are technically good enough for an assessment. Is that not the case? If so, it could be necessary to retake one or more additional images. Otherwise, this is the end of the procedure.
The breast X-rays will be sent to two radiologists. They will assess the images separately.

5. The results

You will receive a letter containing the results within 10 working days. Is your screening planned on the same day as other women in your street? It is possible that you do not receive the letter with the result on the same day as the other women. This says nothing about the results. You do not have to worry about that.

Do you want to see what happens during the screening?
Please watch the video showing all the steps on
www.bevolkingsonderzoekborstkanker.nl

Useful information:

- The screening centre has no toilet facilities.
- Wear a comfortable top that is easy to take off.
- The screening centre employs both male and female employees.
- Do not put cream, powder or lotion on the upper part of your body.
- You are allowed to use deodorant.
- Do you use zinc ointment on your breasts? You must stop using this two to three weeks before the screening.

Remember to bring the following
- The letter that you received with this brochure. Write down the name and contact data of your GP on the letter.
- Your proof of identity (passport, ID card or driving licence).

Why do we use X-rays?

X-rays show abnormalities

X-rays allow us to examine your breast tissue. It enables us to detect any abnormalities that might be breast cancer. X-rays are still the best way to detect breast cancer in the screening programme.

We can detect breast cancer at an early stage

X-rays enable us to see abnormalities that you have not noticed yourself. The sooner we detect breast cancer, the bigger the chance of a successful cancer treatment.

We try to limit the radiation needed for each image
X-rays cause radiation. You are also exposed to radiation in daily life. In the Netherlands, this is approximately 2.6 millisievert per year. We take two X-rays of each breast. The total of four X-rays causes radiation of approximately 0.6 millisievert. Radiation can cause cancer, but the risk of these small amounts is very small.

How do we assess the X-rays?

Radiologists assess the X-rays

The X-rays are examined by two radiologists. They work separately. Radiologist are specialised in detecting abnormalities in X-rays. An abnormality can be the beginning of breast cancer.

An X-ray of your breast is called a 'mammogram'. 'Mamma' is the Latin word for female breast.

The screening is particularly useful if you take part every time

Have you taken part in previous screenings? In that case, the radiologists will compare the new images with the images taken at the previous examination. This allows them to notice any differences. This might help to detect abnormalities at an early stage.

It is up to you whether or not you participate

Just as with any other medical test, the screening has advantages and disadvantages. It is up to you whether or not you participate. It is important to take the following elements into consideration:

You could get worried
There is a chance you might be referred to the hospital, for instance, because an abnormality was detected in one of the images. Or because the images do not show enough information. This does not necessarily mean that you have breast cancer. But it could cause you some anxiety.

You run the risk of unnecessary treatment
In some women, breast cancer develops so slowly that it would not have affected them during their lifetime. However, breast cancer is nearly always treated. Has breast cancer been detected at the hospital? This could mean that you will be treated for cancer, even if it would not have affected you.

The screening does not provide complete certainty
Screening detects approximately seven out of every ten cases of breast cancer. If the X-rays do not show anything, there is still a small chance that you have breast cancer.

You can develop breast cancer in the period between two screening rounds
You will receive an invitation for screening every two years. It is possible that you develop breast cancer in the period between two screening rounds. That is why it is still very important to visit your GP if you notice any changes in your breasts.

i For more details about the screening programme go to www.bevolkingsonderzoekborstkanker.nl.

Would you prefer not to participate in the screening programme?
In that case, please complete the sign-out form on the reverse of this leaflet.

For women from 50 to 75 years of age

You can participate from the age of 50

There are two reasons why you can participate from the age of 50:
- Breast cancer occurs more frequently in women over 50. Eight in ten women who develop breast cancer are over 50 years of age.
- Breasts of younger women often contain more glandular and connective tissue. This limits the efficacy in detecting breast cancer with X-rays. This tissue is also more susceptible to radiation.

You will receive an invitation every two years

You can take part in the screening programme every two years. More frequent imaging has more disadvantages than advantages for most women.

The population screening programme stops after you reach the age of 75

In women over 75, breast cancer usually develops slowly. At this age, it is very unlikely that we detect breast cancer that will be the cause of death. Participation in the population screening programme could lead to unnecessary treatment of cancer for these women.
You will receive an invitation from the age of 50 until the year you turn 76.

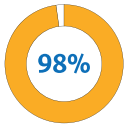
The Health Council makes recommendations
The government determines the target group for the population screening programme. This happens after recommendations from the Health Council, who carefully weighs all benefits and disadvantages. The Health Council has recommended not to change the ages for the population screening programme for the time being.

What can the results be?

After the screening, you will receive a letter containing the results within 10 working days. You can get **one of the following three** results:

1. No abnormalities found

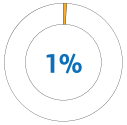
No signs of breast cancer were detected on the X-rays. You can take part again in the screening programme in two years. The screening does not provide complete certainty. There is a chance that existing breast cancer is not discovered. Breast cancer could also develop in the period between two screening rounds. Have you noticed any changes in your breast? If so, please contact your GP. The medical terms for this result are BI-RADS 1 and BI-RADS 2.



98 out of 100 women get this result

2. No sufficient information

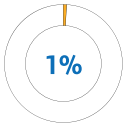
In this case, the X-rays have not provided enough information to allow a proper assessment. Further assessment in the hospital is required. This could mean an additional X-ray or an ultrasound scan. In most cases, there is nothing to worry about. The medical term for this result is BI-RADS 0.



1 out of 100 women gets this result

3. An abnormality has been detected

The X-rays show an abnormality that could be breast cancer. Further assessment in the hospital is required. This could mean an X-ray or an ultrasound scan. In most cases, a small tissue sample is taken from the breast. It does not necessarily mean that you have breast cancer. The medical terms for this result are BI-RADS 4 and BI-RADS 5.



1 out of 100 women gets this result

Your data

We obtained your details from the local authority

We have obtained your name, address and date of birth from the local authority. If you take part in the population screening programme, you give permission to use your details and the results of the screening for the population screening programme and any follow-up testing at the hospital.

We can consult your GP

Do you require follow-up testing because the images do not show enough information? Or because an abnormality was detected in one of the images? If so, we will contact your GP. The GP will provide a referral to the hospital.

Your privacy is protected

We use the results from the test to continue to improve the screening. For this goal, we will exchange data with research and care facilities. We always comply with the legislation that protects your privacy. Facilities that do not contribute to the improvement of the population screening programme cannot get access to the data.

You can object

Would you prefer us not to share your details or test results with care and research facilities? If so, you can object to this. You can request a form from the screening organisation in your area for this purpose. You can also download one from the website of your screening organisation.
Go to www.bevolkingsonderzoekborstkanker.nl for more information.
This website also offers more information about privacy and filing an objection.

More information

For more information about the advantages and disadvantages, breast cancer and the screening, please visit www.bevolkingsonderzoekborstkanker.nl

Do you have any questions, suggestions, or complaints?

If you have questions, suggestions or complaints, please contact the screening organisation in your region. The screening organisation coordinates the screening on behalf of the government. The phone number is given in the letter, or on your screening organisation's website.

1. Screening Programme 'Noord'
www.bevolkingsonderzoeknoord.nl

2. Screening Programme 'Oost'
www.bevolkingsonderzoekoost.nl

3. Screening Programme 'Zuid'
www.bevolkingsonderzoekzuid.nl

4. Screening Programme 'Zuid-West'
www.bevolkingsonderzoekzuid-west.nl

5. Screening Programme 'Midden-West'
www.bevolkingsonderzoekmidden-west.nl

bevolkingsonderzoek

A screening is a free medical examination for early detection of a disease. The government provides three screening programmes for cancer: These are screenings for cervical cancer, breast cancer, and bowel cancer. These diseases can be detected at an early stage, even before someone shows symptoms.

Information in other languages

This information is also available in Dutch, Turkish and Arabic at:
www.bevolkingsonderzoekborstkanker.nl/vertalingen

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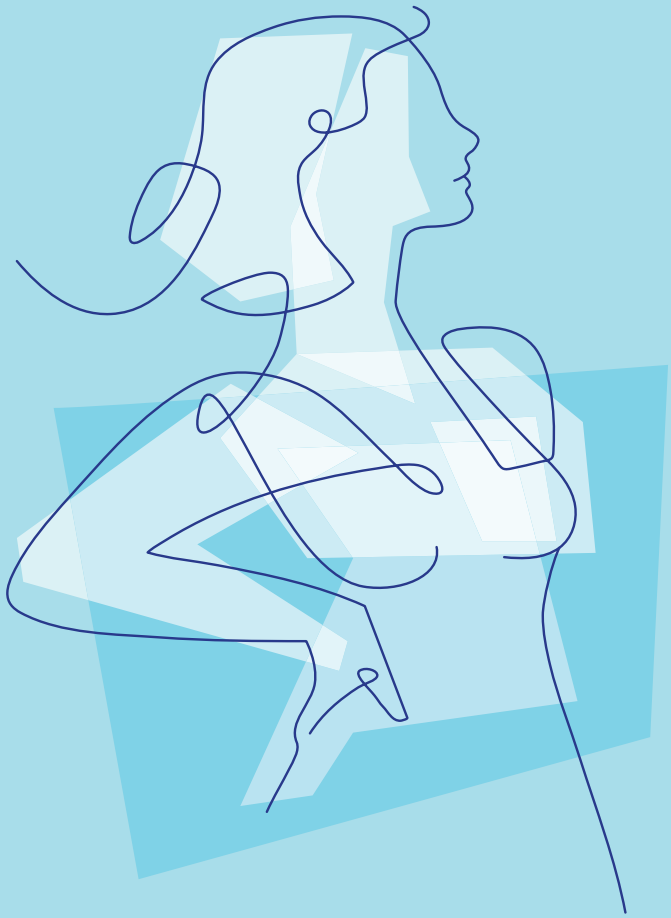
Appendix Table 1 subgroup data for the first-time invitees on explicit attitudes, knowledge, intention to participate, attendance, and informed choice of breast cancer screening at baseline and follow-up, split for leaflet and control group (n (%)).

	Baseline	**Follow-up**		
		Leaflet	**Control**	**P-value**
	n=114	n=58	n=56	
Explicit attitudes				**0.038**
Positive	111 (97)	58 (100)	52 (93)	
Negative	3 (3)	0 (0)	4 (7)	
Missing	*0*	*0*	*0*	
Levels of knowledge (0-11)				
Mean (range)	8.9 (2 – 11)	10.0 (4–11)	8.7 (2 – 11)	**<0.001**
Sufficient knowledge (≥8) n (%)	90 (80)	53 (93)	43 (77)	**0.016**
Missing	*1*			
Intention to participate				**0.012**
Positive	107 (95)	58 (100)	48 (86)	
Neutral	5 (4)	0 (0)	7 (13)	
Negative	1 (1)	0 (0)	1 (2)	
Missing	*1*	*0*	*0*	
Participation				0.214
Had screening test	81 (83)	42 (88)	39 (78)	
Did not have screening test	17 (17)	6 (13)	11 (22)	
Missing	*16*	*10*	*6*	
Informed choice				**0.017**
Yes, informed decision to have screening	63 (64)	39 (81)	28 (55)	
Yes, informed decision to not have screening	2 (2)	0 (0)	1 (2)	
No, not an informed decision	34 (34)	9 (19)	22 (43)	
Missing	*15*	*10*	*5*	



8

Health-related Quality of Life using the EQ-5D-5L: normative utility scores in a Dutch female population

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ABSTRACT

Purpose

Normative utility scores represent the health related quality of life of the general population, are of utmost importance in cost-effectiveness studies and should reflect relevant sexes and age groups. The aim of this study was to estimate EQ-5D-5L normative utility scores in a population of Dutch females, stratified by age, and to compare these scores to those of female populations of three other countries.

Methods

Dutch women completed the EQ-5D-5L online between January and July 2020. Mean normative utilities were computed using the Dutch EQ-5D-5L value set, stratified by age, tested for differences using the Kruskall-Wallis test, and compared to normative utility scores of female populations elsewhere. Additionally, to support the use of the Dutch EQ-5D-5L data in other settings, normative utility scores were also calculated by applying the value sets of Germany, United Kingdom and United States.

Results

Data of 9037 women were analyzed and the weighted mean utility score was 0.911 (SD 0.155, 95% CI 0.908–0.914). The mean normative utility scores differed between age groups, showing lower scores in older females. Compared to other normative utility scores of female populations, Dutch mean utilities were consistently higher except for age groups 18-24 and 25-34. With the three country-specific value sets, new age-specific mean normative utility scores were provided.

Conclusion

This study provides mean normative utility scores of a large cohort of Dutch females per age group, which were found to be lower in older age groups. Utility scores calculated with three other value sets were made available.

INTRODUCTION

The effectiveness of a health care intervention or strategy can be measured in a variety of ways. A commonly used method is measuring and comparing the Health-related Quality of Life (HrQoL) between groups. HrQoL is a measure of the impact of disease and treatment on an individuals' disability and daily functioning.[1] It includes factors that are part of an individual's health, without non-health aspects such as economic circumstances, and is often used in cost-effectiveness studies.[2] HrQoL outcomes are gathered using questionnaires and respondents' answers can be converted into a single utility score, usually between 0 and 1, that reflects the personal desirability of an individual's health state at a particular point in time.[2] The EQ-5D-5L is often recommended as the instrument to obtain utility scores.[3] To enable the conversion for EQ-5D-5L outcomes, pre-defined country-specific value sets have been developed to this aim.[4]

In cost-effectiveness studies, utility scores are used to calculate quality adjusted life years (QALY's) for all relevant health states. If utility scores are not available for these health states, assumptions about such utilities have to be made. However, assumptions are sub-optimal compared to objectively measured utilities as this influences cost-effectiveness ratios and ultimately decision making.[5,6] Besides utilities for disease specific health states, also utilities for the general population are considered to be relevant. These so-called 'normative utility scores' can be used as a comparator for health profiles of patients based on subgroups with similar age and gender. Additionally, they can be used to compensate for a loss in HrQoL due to factors that are not caused by the disease or intervention of interest.[7] Currently, many cost-effectiveness studies made the assumption of a utility of 1 (reflecting perfect health) for the general population. However, Versteegh et al. obtained utilities in a general Dutch population and the results suggested that utilities of the general population tend to be below 1.[8] This means that cost-effectiveness studies may overestimate the health of the general population, and thereby overestimate the loss in utility score caused by a disease or intervention. Therefore, up to date normative utility scores are needed to be used in cost-effectiveness studies.

Other countries have calculated normative utility scores using the EQ-5D and showed differences between genders.[9-11] In studies on women's health, using gender-specific normative EQ-5D utility scores of females only may be more accurate than population norms. Janssen et al. published EQ-5D index value population norms for 20 countries in Europe including the Netherlands.[12,13] Data of 2367 people, identified between 2001 and 2003, was used to calculate age stratified normative utility scores.[14] However, these results were based on the EQ-5D-3L, and the Dutch normative data for the EQ-5D-5L

that was published thereafter, was not classified by gender.[8,13] This is a drawback for cost-effectiveness studies among only male or female populations.

Therefore, the aim of this study was to obtain EQ-5D-5L normative utility scores in a female Dutch cohort, stratified by age. In addition, these normative utility scores were compared to normative utility scores of female cohorts of other countries. Furthermore, three different country-specific value sets were applied to the answers of the EQ-5D-5L of the Dutch cohort. This analysis was conducted to illustrate the impact of using different value sets on age-specific mean normative utility scores, and to enable the use in cost-effectiveness studies in populations for which country-specific normative utility scores for women are not available.

METHODS

Study participants

Data were collected in a study that initially obtained normative data for the Breast-Q (a breast cancer specific quality of life questionnaire).[15] Dutch women were invited to complete a web-based survey that was disseminated through social media platforms of the Erasmus Medical Center between January and July 2020. Because the researchers focused on breast cancer, normative data should be based on women unencumbered by the diagnosis of breast cancer. Therefore, women who were previously diagnosed with breast cancer were excluded from the survey.

Besides the Breast-Q, the survey also included the EQ-5D-5L. This current study made use of this EQ-5D-5L data.

Health related Quality of Life measured with the EQ-5D-5L

The Dutch version of the EQ-5D-5L was used to measure HrQoL.[3] The EQ-5D-5L is a non-disease-specific instrument, and consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with five levels of functioning, ranging from no problems to extreme problems. Eventually, 3125 different health states can be provided based on these five dimensions. A quality-adjustment weight or "utility" is a number anchored at 0 and 1, with "perfect health" carrying a weight of 1 and death carrying a weight of 0. A utility score below 0 is possible when a health state is valued worse than death. Utilities can be calculated after application of pre-defined values to a specific health state as indicated by a respondent. Utilities in this study were computed according to the Dutch tariffs for the EQ-5D-5L as established by Versteegh et al.[8]

Statistical analysis

Descriptive statistics, including standard deviations and confidence intervals, were calculated to present the mean normative EQ-5D-5L index scores per age group. Age was categorized into seven subgroups; 18-24, 25-34, 35-44, 45-54, 55-64, 65-74 and ≥ 75 years. A weighted mean normative utility score was calculated taking into account the population size per age group of the Dutch population in 2020 (see Appendix, Figure 1).[253] Because the data were not normally distributed, the Kruskal-Wallis test was used to compare mean utility scores between all age-groups. The data analyses were performed using IBM SPSS Statistics (Version 25) and R (Version 1.2).

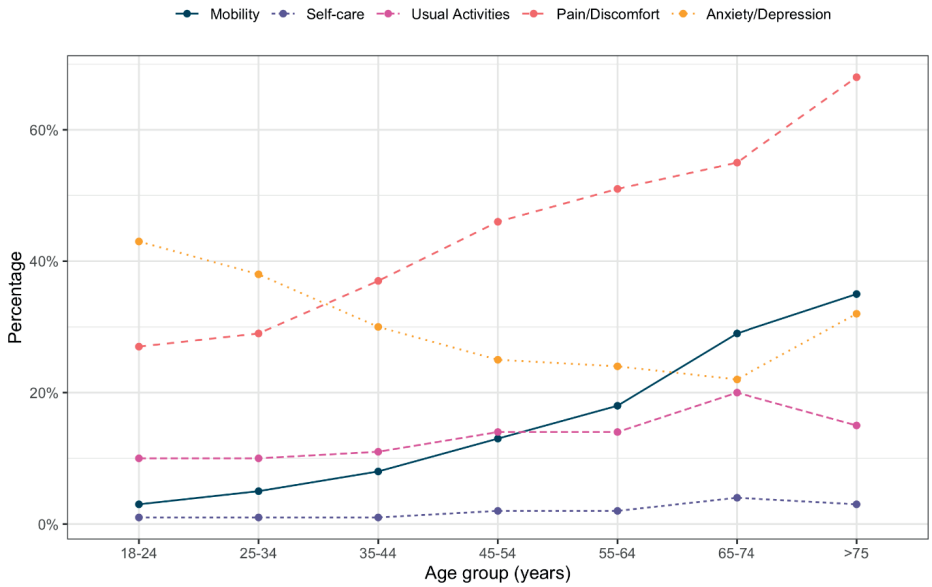

Figure 1 Frequencies of having 'any problems' (level 2-5) in the EQ-5D-5L dimensions based on age group.

Comparisons with three other countries

The mean normative utility scores per age-group were compared to normative utility scores for female populations in studies performed in Germany, South Australia, and the United States (US).[9-11] Furthermore, the country-specific value sets used in these studies (i.e. the value sets of Germany, the United Kingdom (UK) and the US) were also applied to the EQ-5D-5L data to convert them into utility scores.[17-19]

RESULTS

The total sample included 9037 females with a median age of 46.0 years (range 18-90 years). According to the responses of the individual EQ-5D-5L dimensions, most health problems were identified in the pain/discomfort (41.2%) and anxiety/depression (29.5%) dimension (Table 1). The anxiety/depression dimension showed relatively high percentages of any health problems (level 2-5) in the younger age-groups, which decreased with increasing age. Health problems in the other dimensions increased when becoming older, which was most evident in the mobility dimension (Figure 1). The mean utility score was 0.917 (SD 0.110, 95% CI 0.915 – 0.920) with a left-skewed distribution, as 44.7% had a utility score of 1 (n = 4037). The weighted mean utility score was 0.911 (SD 0.155, 95% CI 0.908 – 0.914).

Table 1 Prevalence of EQ-5D-5L responses for the Dutch female normative population (n=9037), stratified by age group.

	Mobility		**Self-care**		**Usual Activities**		**Pain/Discomfort**		**Anxiety/Depression**	
Level	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All ages										
1	8016	88.7	8899	98.5	7900	87.4	5328	59.0	6379	70.6
2	719	8.0	109	1.2	836	9.3	2871	31.8	2174	24.1
3	241	2.7	24	0.3	237	2.6	701	7.8	413	4.6
4	51	0.6	3	0.0	60	0.7	123	1.4	63	0.7
5	10	0.1	2	0.0	4	0.0	14	0.2	8	0.1
Any problems		*11.4*		*1.5*		*11.9*		*41.2*		*29.5*
Age 18-24										
1	614	96.8	628	99.1	573	90.4	460	72,6	361	56.9
2	15	2.4	6	0.9	52	8.2	146	23.0	203	32.0
3	4	0.6	0	0.0	7	1.1	25	3.9	58	9.1
4	1	0.2	0	0.0	2	0.3	2	0.3	9	1.4
5	0	0.0	0	0.0	0	0.0	1	0.2	3	0.5
Any problems		*3.2*		*0.9*		*9.6*		*27.4*		*43*
Age 25-34										
1	1498	95.5	1557	99.2	1419	90.4	1112	70.9	981	62.5
2	47	3.0	7	0.4	114	7.3	368	23.5	470	30.0
3	19	1.2	4	0.3	26	1.7	72	4.6	96	6.1
4	4	0.3	0	0.0	10	0.6	16	1.0	20	1.3
5	1	0.1	1	0.1	0	0.0	1	0.1	2	0.1
Any problems		*4.6*		*0.8*		*9.6*		*29.2*		*37.5*
Age 35-44										
1	1902	91,7	2048	98.7	1841	88.8	1306	63.0	1430	68.9
2	124	6,0	23	1.1	173	8.3	611	29.5	545	26.3
3	39	1,9	3	0.1	47	2.3	133	6.4	88	4.2
4	7	0,3	0	0.0	13	0.6	22	1.1	10	0.5
5	2	0,1	0	0.0	0	0.0	2	0.1	1	0.0

Table 1 Prevalence of EQ-5D-5L responses for the Dutch female normative population (n=9037), stratified by age group. (*continued*)

	Mobility		**Self-care**		**Usual Activities**		**Pain/Discomfort**		**Anxiety/Depression**	
Any problems		*8.3*		*1.2*		*11.2*		*37.1*		*30.5*
Age 45-54										
1	2416	87.3	2715	98.1	2348	86.2	1488	53.8	2083	75.3
2	258	9.3	42	1.5	277	10.0	976	35.3	577	20.9
3	70	2.5	8	0.3	81	2.9	246	8.9	94	3.4
4	18	0.7	1	0.0	23	0.8	48	1.7	12	0.4
5	5	0.2	1	0.0	2	0.1	9	0.3	1	0.0
Any problems		*12.7*		*1.8*		*13.8*		*46.2*		*24.7*
Age 55-64										
1	1285	82.0	1541	98.3	1342	85.6	774	49.4	1194	76.1
2	199	12.7	21	1.3	162	10.3	603	38.5	302	19.3
3	70	4.5	6	0.4	54	3.4	166	10.6	62	4.0
4	12	0.8	0	0.0	9	0.6	24	1.5	9	0.6
5	2	0.1	0	0.0	1	0.1	1	0.1	1	0.1
Any problems		*18.1*		*1.7*		*14.4*		*50.7*		*24.0*
Age 65-74										
1	279	71.4	377	96.4	312	79.8	177	45.3	307	78.5
2	68	17.4	9	2.3	55	14.1	152	38.9	68	17.4
3	35	9.0	3	0.8	20	5.1	51	13.0	13	3.3
4	9	2.3	2	0.5	3	0.8	11	2.8	3	0.8
5	0	0.0	0	0.0	1	0.3	0	0.0	0	0.0
Any problems		*28.7*		*3.6*		*20.3*		*54.7*		*21.5*
Age >75										
1	22	64.7	33	97.1	29	85.3	11	32.4	23	67.6
2	8	23.5	1	2.9	3	8.8	15	44.1	9	26.5
3	4	11.8	0	0.0	2	5.9	8	23.5	2	5.9
4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Any problems		*35.3*		*2.9*		*14.7*		*67.6*		*32.4*

EQ-5D-5L answer levels = level 1 (no problems); level 2 (slight problems); level 3 (moderate problems); level 4 (severe problems); level 5 (inability / extreme problems).
Any problems = percentage of any problems (level 2-5) in the EQ-5D-5L dimensions according to age group.

Primary outcome

The mean normative utility score ranged from 0.929 (SD 0.102) (age group 25-34) to 0.881 (SD 0.081) (age group >75). The highest mean normative utility scores were found in the three youngest age groups (between age 18 and 44 years) (Table 2). After age 45, mean normative utilities decreased with increasing age with lowest mean utility scores in the oldest age group (>75 years). The Kruskal-Wallis test revealed that there were statistically significant differences in mean normative utility scores between all age groups ($p < 0.001$). However, absolute differences were small.

Table 2 Mean normative scores, standard deviations, and confidence intervals of four different utility value sets applied on the Dutch female normative EQ-5D-5L data (n=9037)

		Dutch value set (Versteegh et al. 2016)		**German value set** (Ludwig et al. 2018)		**UK value set** (Devlin et al. 2018)		**US value set** (Pickard et al. 2019)	
Age group	**n**	*Mean (SD)*	*95% CI*	*Mean (SD)*	*95% CI*	*Mean (SD)*	*95% CI*	*Mean (SD)*	*95% CI*
18-24	634	.927 (.091)	.920-.934	.953 (.075)	.947-.959	.933 (.083)	.926-.939	.934 (.094)	.926-.941
25-34	1569	.929 (.102)	.924-.934	.953 (.087)	.949-.957	.935 (.094)	.930-.940	.935 (.110)	.929-.940
35-44	2074	.925 (.102)	.921-.930	.950 (.087)	.946-.954	.933 (.095)	.929-.937	.931 (.114)	.926-.936
45-54	2767	.913 (.120)	.908-.917	.939 (.106)	.935-.943	.925 (.106)	.921-.929	.918 (.131)	.913-.923
55-64	1568	.907 (.112)	.902-.913	.936 (.098)	.931-.941	.919 (.102)	.914-.925	.910 (.127)	.904-.916
65-74	391	.890 (.131)	.877-.903	.919 (.117)	.859-.888	.901 (.123)	.889-.914	.884 (.154)	.869-.900
>75	34	.881 (.081)	.854-.910	.918 (.066)	.895-.941	.894 (.084)	.864-.923	.877 (.108)	.839-.915

n = number of participants per age-group, SD = standard deviation, CI = confidence interval.
UK = United Kingdom, US = United States.

Comparisons with three other countries

Compared to published normative utility scores for female populations in Germany, the US and South Australia, our mean normative utilities were consistently higher except for age groups 18-24 and 25-34 (Table 3).

The mean utility scores were recalculated after applying the country-specific value sets of Germany, the UK, and the US to the EQ-5D-5L answers of our Dutch cohort. This resulted in slightly higher mean utility scores for all age groups with all three value sets (Table 2). The mean utility scores were the highest when the German value set was applied.

Table 3 Mean normative utility scores based on the EQ-5D-5L in other female populations stratified by age group

	The Netherlands		**Germany Grochtdreis et al. (2019)**		**South Australia McCaffrey et al. (2016)**		**United States Jiang et al. (2021)**	
Age group	**n**	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*
18-24	634	0.93 (0.09)	230	0.94 (0.08)	226	0.95 (0.08)	53	0.93 (0.09)
25-34	1569	0.93 (0.10)	363	0.92 (0.10)	224	0.95 (0.11)	130	0.92 (0.11)
35-44	2074	0.93 (0.10)	386	0.88 (0.17)	241	0.91 (0.13)	95	0.85 (0.21)
45-54	2767	0.91 (0.12)	494	0.86 (0.19)	253	0.87 (0.16)	102	0.81 (0.24)
55-64	1568	0.91 (0.11)	399	0.86 (0.20)	226	0.88 (0.15)	67	0.83 (0.21)
65-74	391	0.89 (0.13)	346	0.85 (0.25)	193	0.87 (0.16)	57	0.82 (0.22)
>75	34	0.88 (0.08)	366	0.77 (0.31)	122	0.82 (0.15)	61	0.83 (0.18)
Total	**9037**	**0.92 (0.11)**	**2584**	**0.86 (0.20)**	**1486**	**0.90 (0.14)**	**565**	**0.86 (0.19)**

n = number of participants per age-group, SD = standard deviation, SE = standard error.

DISCUSSION

We obtained normative utility scores by using the EQ-5D-5L in a sample of 9037 Dutch females and found relatively high utility values for Dutch females aged 18 to >75 years old. In general, the mean normative utilities were lower in the older age groups although absolute differences were small. Applying the country-specific value sets of Germany, UK and US to the EQ-5D-5L answers of our Dutch sample resulted in consistently higher mean utility scores in all age groups as compared to the mean utility scores calculated with the Dutch value set.

Our mean normative utility scores in the younger age groups were slightly lower than previously found in female populations of other countries.[9-11] This difference may be caused by the sampling method. Young people that are less healthy may spend more time on their computer, mobile phones or social media than healthy adolescents who are possibly able to do more activities. Therefore, they might have been more likely to encounter the study invitation and more inclined to complete a questionnaire on their health. The normative utility data of female populations of other countries was collected between 2013 and 2017.[9-11] The lower Dutch utilities in the younger age groups compared to those of previous studies might be explained by an increase in mental health problems in adolescents over the last years as observed in the Netherlands.[20] The data of this study was collected during the start of the COVID-19 pandemic, which also led to more anxiety and mental health issues in particularly in females and adolescents, and may have contributed to lower utility scores.[21] Besides, it appears as if the use of the Dutch value set is partially responsible for the differences in utility scores in younger age groups (up to 35 years), because the differences in utility becomes smaller when the German, UK, and US value sets were used. In contrast, our mean normative utility scores in the older age groups were higher than those in female populations of other countries. Particular in these age groups, the differences were enlarged by the use of the German, UK and US value sets. That is, these differences cannot be explained by the value sets themselves.

The oldest age group (>75 years) showed a relatively high mean normative utility, as none of the participants scored level four and five across all dimensions. This might indicate that older Dutch women have a relatively good quality of life, and possibly better than older women elsewhere. In contrast to a recently published Russian article reporting normative utility scores, Dutch women did not show many problems in the self-care dimension for all age groups.[22] In the current study, the frequency of having any problems in the anxiety/depression dimension decreased with increasing age, but was consistent across all age groups in the Russian population. Although the pattern of having any problems in the mobility dimension was similar in both studies, the frequency in the older age group was considerably

higher in the Russian population.[22] However, the high mean normative utilities may also be related to most participants being between 75 and 80 years of age, and no one being older than 90 years. Because more health issues appear with increasing age, this may explain the differences with other studies if they included older participants.[22-24] In addition, the sample of older participants (n=34) was relatively small, which reduces the generalizability. Another explanation is the use of social media as a recruitment method, which may have caused some selection bias. Older females that are able and willing to complete a questionnaire through an online survey are potentially in better health.[25] On the other hand, internet is easily accessible in the Netherlands and internet use is higher than in most other western countries, also in older people.[26] Interestingly, Jiang et al. has shown differences in outcome between face-to-face and online sampling, with higher EQ-5D-5L index scores in the face-to-face population for most age groups.[9] However, the index scores of the older participants (i.e. above the age of 65) were slightly higher in the online population.[9]

We found statistically significant differences in mean normative utility scores between the age groups. However, we expected larger age-specific absolute differences beforehand based on results of previous normative studies (both males and females) in the Netherlands.[27] Nevertheless, we recommend to use age and gender specific reference values, as they are important for cost-effectiveness studies and can have a substantial effect on outcomes.[5,6] It would be interesting to investigate to what extent our age-specific values alter the outcomes of cost-effectiveness analyses. To note, our normative utility scores are mainly intended to answer women-specific research questions, and they might not be directly comparable to future normative utility scores of Dutch males as they are not generated from the same sample.

The key strengths of our study are the use of the EQ-5D-5L to obtain normative utility scores and the large sample size. The EQ-5D-5L is more sensitive than the EQ-5D-3L version which has several limitations (e.g. ceiling effects in patient populations, non-detection of small differences or changes in patients with mild conditions).[28-30] Furthermore, the sample size of our cohort was substantially larger (at least three times) than the samples in previous studies, and in combination with the more sensitive 5-level version of the EQ-5D, our study may have resulted in more reliable outcomes.[9-12] Another strength is that we provide age-specific mean utility scores specifically for women. These could be used an up-to-date reference point in research and Dutch health policy evaluations, such as breast and cervical cancer screening strategies, and health policies for pregnancy and childbirth. Importantly, our study did not gather demographic data which makes it difficult to state anything about the representativeness of the population. We used a web-based survey that was disseminated through the institutes' social media platforms, which are all accessible for the general population. To be able to complete the survey, access

to internet was required. Especially in the Netherlands, internet use has increased over the last decade and is nowadays extremely high as 95% of total population has access to internet.[31] This makes the internet-user population very similar to the general population. Even back in 2013, internet was the main source to search for health information (83%) in the Netherlands, and social media is frequently used for this purpose.[32] The percentage of social media use is more than 90% for the age group of 18-54 years, and between 76% and 89% in the age group of 55-64 years of the Dutch population.[33] Also, due to working from home and the lockdown caused by the COVID-19 pandemic, Dutch people may have spent more time on social media which increased the responsiveness to the survey. Although we cannot assume that all female internet-users have seen our survey, we believe that the survey reached a large and representative part of the Dutch female population. Despite our large sample size the group of elderly females was relatively small. In other countries where internet availability is less developed, using this sampling method might be more of an issue because certain populations are possibly left out.

To date, it is unclear if and to which extent utility measurements on a national level can be generalized to other countries. However, there are differences between the country-specific value sets even between countries that were expected to have quite similar populations, socioeconomic status, health systems, or attitudes to health.[13] Therefore, using a country-specific value set is encouraged.[34,35] In this study, a subset of value sets of three other countries was used to calculate utility scores based on the answers to the EQ-5D-5L of our Dutch female cohort. This was done to illustrate the impact of using different value sets on age-specific mean normative utility scores, and also to provide age-specific mean normative utility scores to be used in cost-effectiveness studies in countries of which country-specific normative utility scores for women are lacking. For example, if a breast cancer study would be conducted in the UK, researchers probably prefer to use the UK value set to determine the utilities in patients. In order to allow for proper comparisons with the general population, they can also best use normative utilities calculated with the UK value set. If age-specific mean normative utility scores for women in the UK are not available, the normative utility scores calculated with the UK value set in this study may be a good alternative. Reporting the normative utility scores for different value sets enlarges the applicability in multiple international studies.

Conclusions

In this study, we presented age specific normative utility scores for the EQ-5D-5L in Dutch females using different value sets. We found lower mean normative utilities in older age groups. Relatively high normative utility scores were found in all age groups, compared to those in other female populations. Furthermore, utility scores were calculated with value sets of three other countries which can be used as normative comparisons in international patient populations.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LMK and MEC. The first draft of the manuscript was written by LMK and MEC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The data are not publicly available but are available for researchers that wish to apply their own country-specific EQ-5D-5L value set on the current dataset. Data shall only be shared with researchers upon reasonably request, at the discretion of the principal investigator.

Conflict of interest

The authors have no conflict of interest to declare that are relevant to the content of this article.

Ethical approval

Formal approval from the local Medical Ethics Review Committee was waived as the Dutch Medical Research (Human Subjects) Act did not apply to this study.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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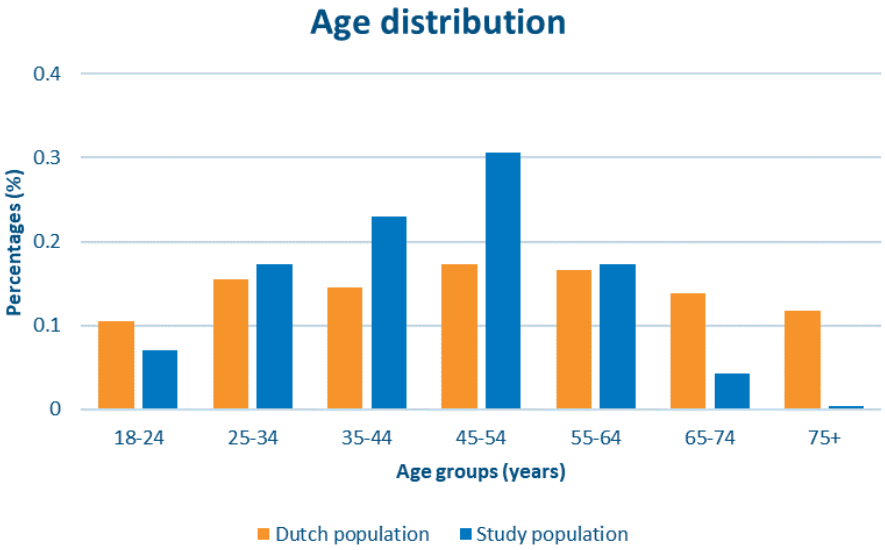
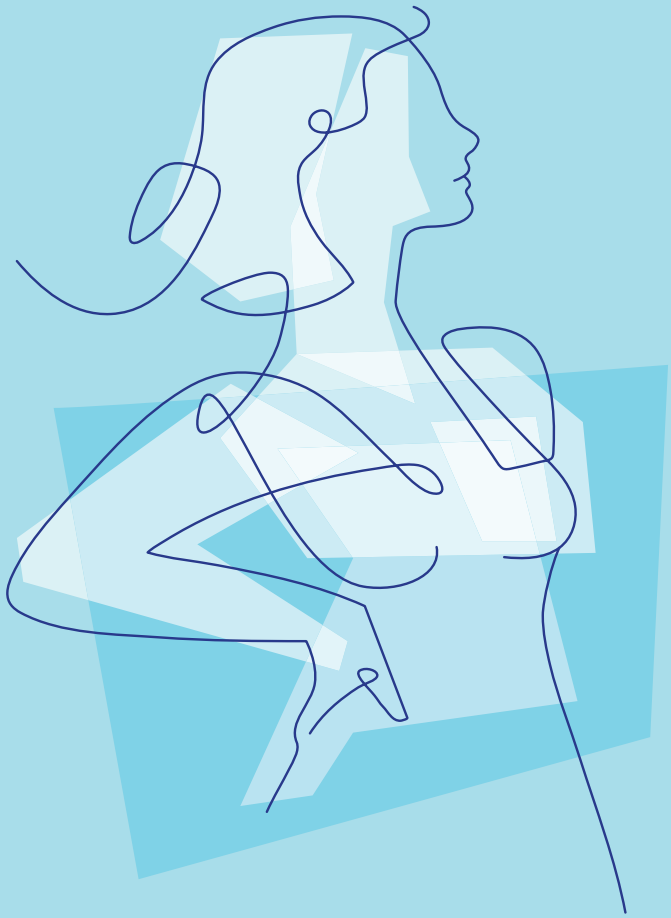
APPENDIX



Appendix Figure 1 Age group distribution for this current cohort (n = 9037) and the female Dutch population in 2020 (n = 7.1 million) used for the weighted mean normative utility score calculation.



Chapter under embargo

9

Health utility values of breast cancer treatments and the impact of varying quality of life assumptions on cost-effectiveness

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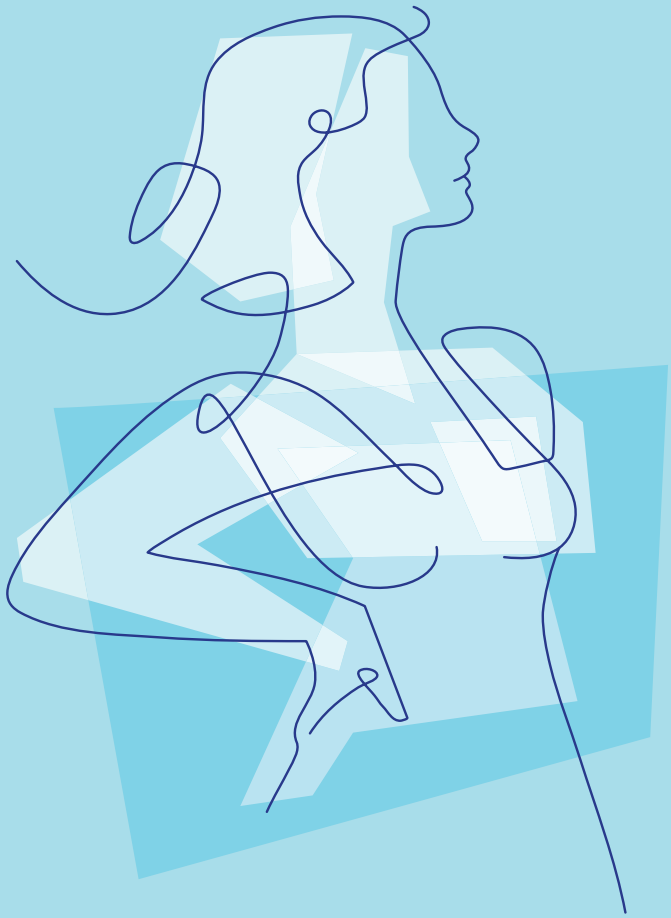
Submitted for publication



10

General discussion

MAIN FINDINGS

Part 1: Effectiveness of breast cancer screening

The aim of breast cancer screening is to detect and treat early stage breast cancer in asymptomatic women to decrease the mortality from the disease and allow for less invasive treatment thereby increasing life expectancy and quality of life. Multiple studies have shown that breast cancer screening indeed reduces breast cancer mortality.[1-3] In **chapter 2** of this thesis, we examined the potential gains in breast cancer mortality reduction that can be accomplished in Europe if breast cancer screening uptake would be optimised. Using data from between 2014 and 2017, linear extrapolation was applied to mortality reduction estimates based on best estimates for different regions in Europe (north: 33%, south: 50%, west: 58%) to calculate breast cancer deaths already prevented and breast cancer deaths potentially preventable with complete coverage and full participation when screening for the ages 50-69.[1,4-6] Throughout Europe, an estimated 21,680 breast cancer deaths were prevented already annually due to screening and it was estimated that an additional 12,434 can be prevented with a 100% examination rate (i.e. complete coverage and full participation). When looking specifically at the Netherlands, data from 2015 and a mortality reduction of 58% were used to predict the number of deaths already prevented and potentially preventable when only screening women aged 50 to 69. This resulted in approximately 1400 breast cancer deaths already prevented due to screening in 2015, representing 47% of the breast cancer deaths that would have happened without screening. If the participation would increase to 100%, potentially another 350 breast cancer deaths can be prevented. This would lead to roughly 1,750 breast cancer deaths prevented in women aged 50 to 74 in 2015 if screening would only invite women aged 50 to 69 and the participation rate was 100%. In addition, because the Dutch breast cancer screening programme also invites women in the age category 70-74, potentially even more breast cancer deaths are being prevented.

As seen in **chapter 2**, the participation rate has a big influence on the effectiveness of the breast cancer screening programme. In addition to breast cancer screening, the Dutch government also offers screening for cervical and colorectal cancer screening. In **chapter 3**, concurrent participation across these three cancer screening programmes was examined. Around age 55 and age 60, women in the Netherlands are being invited for breast, cervical, and colorectal cancer screening. In the period 2017-2019, 54% of them participated in all three screening programmes, 22% in two, 12% in one, and 12% in none of them. Internationally seen, this is quite high suggesting that in general women in the Netherlands have a positive view towards participating in all three programmes. Furthermore, this study found that women living in areas with higher population density

were less likely and women in higher SES groups were more likely to participate in more screening programmes.

Performance of a screening programme is usually measured per screening examination or calendar year. This is also what is provided in information folders provided to the women upon invitation. However, women in the Netherlands are invited for thirteen breast cancer screening examinations in their life and tend to make a fundamental decision about participation and stick to that.[7] In **chapter 4** we investigated the cumulative risks of having a breast cancer detected via screening and the cumulative risk of receiving a false positive (FP) screening result over multiple breast cancer screening examinations. We found that, when participating in seven screening examinations, the cumulative risk of having a FP result is 9.1% and of having a screen-detected breast cancer is 3.7%. After eleven examinations, we predicted that this increased to 13.5% and 7.1%, respectively. By including this in the information leaflet, we believe that women can make a more informed choice about participation in the screening programme. Furthermore, we found that women who had a FP result participated less often in the next screening round than women who had a true negative (TN) result, while the incidence rate of FP, TP, and interval cancers was higher among women who had a history of FP results. Providing this information to women with a history of FP results could make them more aware of their increased risk which may increase participation in the next round and potentially result in finding more cancers in an earlier stage.

Next to participation rate and detection rate, the length of the interval between two screening rounds also influences the effectiveness of breast cancer screening. During the first wave of Coronavirus disease (COVID-19) and its accompanying lockdown in 2020, many countries disrupted their cancer screening programmes.[8] This led to a one-time elongation in the screening interval. **Chapter 5** of this thesis investigated the effects of this disruption in breast, cervical, and colorectal cancer screening and multiple possible re-start strategies on incidence, mortality and required capacity for screening and follow-up. We found that the effects of a six month screening disruption would have a small effect on cervical cancer incidence and mortality (0.3 additional cervical cancer deaths per 100,000 eligible individuals), but a more substantial effect on breast and colorectal cancer mortality (2.0 and 2.5 additional breast and colorectal cancer deaths per 100,000 eligible individuals, respectively). However, this effect could be avoided almost completely by catching up all missed screening tests on top of continuing the original schedule when restarting screening compared to undisrupted screening. This restart strategy, however, would require a doubling in capacity during the six months after screening was restarted. When this is not possible due to limited capacity, mortality can be limited by restarting screening where the schedule was disrupted and simultaneously increasing the stopping

age with six months, so no last round would be omitted. By doing so, additional mortality could be limited to 1.6, 0.1, and 2.0 additional breast, cervical, and colorectal cancer deaths per 100,000 eligible individuals, respectively.

Besides interval, also the age range of the women invited for screening is a crucial factor for effectiveness. When breast cancer screening was introduced in the Netherlands in 1988, biennial screening for the ages 50 to 69 was chosen as the best strategy.[9] Later on, research showed that screening was effective in women up to 74 years of age.[10-12] Therefore, in 1997, the stopping age was extended to 74. Since then, breast cancer risk factors have increased leading to a higher breast cancer incidence, breast cancer treatment improved, and breast cancer screening improved.[13-17] These changes may have shifted the harm-benefit balance of breast cancer screening which may lead to a different screening strategy to be more beneficial. Furthermore, the Dutch breast cancer screening programme is currently dealing with capacity restrictions which may limit the feasibility of possible screening strategies based on number of screening tests performed per year.[18] **Chapter 6** looked into the cost-effectiveness of 920 different screening strategies differing in screening interval and eligible ages using recent data on incidence, treatment effectiveness and screening effectiveness to investigate optimal screening strategies in the current situation. We found that, using a conservative willingness to pay threshold of €20,000 per quality adjusted life year (QALY) gained, biennial screening for ages 40 to 76 would be most optimal resulting in 33% more breast cancer deaths prevented and 46% more QALYs gained compared to the current strategy. However, this strategy also resulted in 25% more overdiagnoses and 90% more FP results, and required a 34% higher screening capacity than the current strategy. The current Dutch strategy (biennial screening for the ages 50 to 74) was close to, but not on the efficiency frontier. This means that there were other strategies that yielded (slightly) more effect while costing less money. These alternatives were triennial screening for the ages 44 to 71 or 44 to 74 which resulted in 5% and 7% more QALYs gained, respectively, while costs were 5% and 1% lower and the required capacity was 17% and 22% lower. Since a few years, the Dutch breast cancer screening programme has been dealing with a capacity restrain due to a shortage in imaging personnel.[18] This, in combination with the screening disruption due to the COVID-19 pandemic, has led to an increase of the screening interval from on average 24 months towards 36 months for a short period of time. At the moment, the screening organisation is training new employees to restore the required capacity to return to the 24 months screening interval as soon as possible. Given this constraint in screening capacity, expanding the screening population to a wider age range, without extending the interval is not an option at the moment. As an alternative, the triennial screening strategies for ages 44 to 71 or 74 can be considered because they yield more QALYs, less costs, and less capacity than the current biennial strategy.

Part 2: Perspectives of the women

Besides effectiveness, the success of an intervention or programme is determined by how its target population feels about it. In part two of this thesis, the perspectives of the women who are eligible for screening was investigated by looking at attitudes, knowledge, informed choice, and quality of life.

Attitude can be subdivided into explicit and implicit attitude. Explicit attitudes are deliberate and present at the conscious level, while implicit attitudes are unconscious and influence behaviour without people's awareness. The explicit and implicit attitudes of women towards breast cancer screening were investigated in **chapter 7**. Women who were almost due for an invitation to have mammography in the breast cancer screening programme were approached to complete a questionnaire on their knowledge, explicit and implicit attitude, and intentions towards participating in the screening programme. The women who completed the questionnaire received the same questionnaire two weeks later and half of them were then firstly asked to read the information leaflet that accompanies the screening invitation. We found that women who were asked to read the leaflet slightly more often had more knowledge and had a positive explicit attitude than the women who did not receive the leaflet before the second questionnaire. The increase in knowledge was most pronounced in women who were about to be invited for their first round of breast cancer screening. No differences were found in implicit attitude, intention to participate, actual participation, and informed choice. In addition, we looked at correlations and found that implicit associations were not correlated with explicit attitude or attendance. Explicit attitudes were correlated with attendance, but only moderately. This means that women do not make a decision about screening participation based on their implicit attitude. Their decision is based on their explicit attitude, but this does not completely explain participation behaviour, so other factors are involved as well.

A common way to investigate how people experience their health (physically and mentally) is to look at health related quality of life. But to know how much better or worse people undergoing a certain intervention or having a certain disease feel, we need normative utilities from a comparable control group. In **chapter 8** we measured the quality of life of a large cohort of women living in the Netherlands between the ages of 18 and 90 years old. We quantified normative utility scores for these women per 10-year age groups to allow for a fair comparison to women undergoing an intervention or disease in the Netherlands. We found an average normative utility of 0.91 and a declining trend with increasing age. Compared to other normative utility scores of female populations, our mean utilities were consistently higher except for women under 35 years of age.

In **chapter 9** we measured quality of life in women who had breast cancer to establish utility scores for different treatments and at different time points in the treatment period. We found that, compared to normative utilities, women had lower utilities right after diagnosis, which decreased more until twelve months after surgery. However, differences in patterns were observed between age groups and types of treatment. Using these utility scores and the normative utility scores from **chapter 8**, we performed a cost-effectiveness analysis to investigate what the difference in outcomes would be when using the different sets of utilities. We found that using perfect health for normative utilities led to overestimation of the amount of QALYs gained by screening compared to gender and age specific utilities based on real world data of a comparable population. However, the different normative utility sets did not substantially change which strategies were on the efficiency frontier or which strategy was found to be optimal. When using different breast cancer utility sets, we found that differences in QALYs gained were only small and mainly visible when comparing biennial and annual screening strategies. Again the optimal strategy was similar across utility sets, with only a small change in eligible ages in the deviating optimal strategy. Sensitivity analyses on screening and follow-up utilities showed that variation among these utilities did not lead to noteworthy differences in QALYs gained, strategies on the efficiency frontier, and optimal strategies.

LIMITATIONS

The studies performed in this thesis contain limitations. The studies in **chapter 5, 6 and 9** were performed using the microsimulation model MISCAN-Breast and in **chapter 5** also the MISCAN-Cervix and MISCAN-Colon model were used. The MISCAN models are well validated and regularly updated using recent data on population characteristics, possible disease progression, treatment effectiveness, and screening effectiveness.[19-21] Therefore, the models can quite accurately simulate cancer incidence and screening effects over time and the effects of potential changes to the screening programmes. However, the models still rely on some assumptions regarding disease progression and future developments. For example, the models simulate the progression of a tumour, although there is no direct observed data on how fast a tumour grows since all tumours are treated as soon as they are diagnosed. Therefore, assumptions on tumour growth rate have to be made based on time between diagnosis and previous clear mammogram (e.g. during screening), and time between diagnosis and surgery (i.e. without neo-adjuvant therapy). Because there is a lot of high quality data on these indirect progression factors, the assumptions are expected to be quite accurate. This was also shown by the accurateness of the incidence predictions made by the models. In addition, model calculations for future years also depend on assumptions regarding future incidence, treatment effectiveness,

and screening effectiveness and participation rate. Some future trends can be predicted quite well, while others depend on many aspects that are more difficult to predict or can easily be disturbed by unforeseen events. Therefore, sensitivity analyses were performed on factors that yielded the largest uncertainty. Furthermore, in the cost-effectiveness analyses in **chapter 6 and 9** the assumption of a participation rate of 100% was made. Although reaching a participation rate of 100% is practically unrealistic, assuming full participation will lead to results that reflect the full potential of the screening strategy and make it possible to compare the strategies among each other and to literature. Also in **chapter 2** we calculated the impact of increasing coverage and participation to 100% with the aim to calculate the full potential of screening. However, as mentioned in **chapter 7**, we believe informed choice is very important when women decide about participation in screening. Therefore, a participation rate of 100% may not only be practically unrealistic, but also socially undesirable. Taking this into account, sensitivity analyses were performed using age dependent participation rates based on recent data in **chapter 6** and using a maximum of 84% participation as desirable in **chapter 2**.

Also studies without the use of the MISCAN models had some limitations. In **chapters 7, 8, and 9**, questionnaires were used to gather data from participants of the studies. As in all questionnaire studies, this could have led to selection bias because only a specific group of women was asked to participate in the study. This might have been the case in **chapter 8** where only breast cancer patients undergoing surgery were included in the study, while there is a small group of patients who do not get surgery. Furthermore, there could have been selection bias in **chapters 7 and 9,** if a specific subgroup of people was more interested in participating than another subgroup. This could have led to a less representative selection of participants and possibly outcomes that are not completely applicable to the total target population. Nevertheless, the results still gain valuable insights into the effect of the information leaflet and normative and breast cancer utilities. Furthermore, social-desirability bias could have led to a distortion in results. This might, for example, have been the case in the questionnaire from the study in **chapter 7** where we asked women whether they were planning to participate in breast cancer screening if they would be invited soon. Therefore, we also requested data from the screening organisation on actual participation (which was, like we expected, somewhat lower than the intention to participate). Also missing data may have caused some bias if the data was missing not at random. We found that there was quite some missing data in the response test to determine implicit attitude in **chapter 7** which could have led to missing data bias. We found that some participants had technical issues which disturbed a proper working of the test and led to the missing data. Therefore, the percentage of women with a positive implicit attitude may not be representative for the total population, but the analysis on correlation between implicit attitude and other factors was expected not to be affected by

that. The studies in **chapter 3 and 4** were performed using registry data. This minimalised the risk of selection, social desirability, and missing data. However, still some selection and missing data bias could be present, for example in **chapter 3** where only women invited to all three screening programmes were included in the study. This excluded a small subgroup of women who permanently opted out of at least one screening programme.

On top of the assumptions in the MISCAN model, also other types of assumptions were made. In **chapter 2**, for example, we made four assumptions regarding risk of attenders versus non-attenders, regional differences, effect of breast cancer treatment, and relation between examination coverage and breast cancer mortality reduction. These assumptions led to some simplifications, but were necessary because more detailed information was not available for all countries or regions investigated. Specifically for the Netherlands, there is more information available on some of these areas which led to a few differences in assumptions in the MISCAN model compared to the study in **chapter 2**. This difference in assumptions led to a difference in the estimates for the amount of breast cancers prevented due to the screening programme. The MISCAN-breast model predicted the Dutch breast cancer screening programme to prevent around 1,300 breast cancer deaths per year in the period 2023 to 2029, taking into account the increase in screening interval due to the COVID-19 pandemic and shortage in personnel. These results also showed that the amount of deaths prevented increased over time and that without the increase in interval, there would be around 50 additional breast cancer deaths prevented annually in this period. Not taking the increase in interval into account, it can be expected that the estimate from the MISCAN model is slightly higher than in **chapter 2**, because the MISCAN model gave estimates for more recent years and also includes screening for women aged 70 to 74. However, the MISCAN estimates are actually slightly lower than the predictions in **chapter 2**. This difference was mainly caused by differences in assumptions on effectiveness of breast cancer screening on mortality. In **chapter 2**, we assumed the mortality reduction to be 58% in western Europe, while in the MISCAN model multiple assumption and inputs in MISCAN lead to a 40% reduction in breast-cancer mortality due to screening in the same population.

Also the response test in the questionnaire from **chapter 7** depended on some assumptions. In the test, a breast cancer screening, neutral, and non-word prime were used. The screening prime was used to investigate the implicit attitude of the participants on breast cancer screening and the other two primes were added as controls. For the screening prime, we used the word "borstfoto's" (breast photos), because we expected it to be more understandable than words like "mammogram" or "breast X-ray". However, the term "breast photos" may also have other association for some people which may have influenced the results of the response test. Still, we believe that for most women the

chosen prime would be associated with breast cancer screening, especially in the context of the questionnaire in which it was specifically mentioned multiple times that the study was about breast cancer screening. In **chapter 9**, we assumed that the baseline utility of the breast cancer patients (i.e. before they were diagnosed) was equal to the normative utility of their age category as determined in **chapter 8**. On individual level, this may not be accurate for all women, however, on population level this will probably average out well.

FUTURE DIRECTIONS

Screening capacity

Currently, the Dutch breast cancer screening programme is dealing with capacity constraints due to a shortage of imaging personnel.[18] The shortage started approximately in 2019, leading to a slightly increased interval of on average 25 months throughout the country. However, in screening regions Zuid-West and Noord-West the shortages were the worst and intervals increased to 27 months. It was expected that the intervals in all screening regions would slowly increase in the following years. Therefore, a campaign was started to attract and train new personnel to be able to bring the interval back to 24 months by 2027. Unfortunately, the COVID-19 pandemic led to a screening disruption of three months in spring 2020 followed by a restart of the programme with a lower capacity due to safety regulations.[22] This rapidly increased the screening interval to 32 months which remained this high throughout 2021 and the first half of 2022. In the meantime, the training of new employees was successful. Therefore, the screening organisation expects the screening interval to be shortened to 31 months in the second half of 2022 and to 25 or 26 months in 2023. Depending on the number of trainees finishing their education, the reduction in interval is expected to slowly continue towards 24 months in the years following 2023. Using the MISCAN-breast model, we simulated different scenarios with increased screening intervals to inform the RIVM on the impact of the increased intervals and different approaches to decrease these on breast cancer mortality. It looks like the training of new personnel will be able to bring the screening interval back to 24 months within a couple of years. However, the shortage of healthcare personnel is an issue that will probably stay important for many more years. Especially when investigating possible changes to the screening programme, it is important to also take capacity into consideration. Furthermore, research on techniques to reduce the required capacity while maintaining screening quality may relieve capacity constraints or make innovations possible that previously required a too high capacity.

Eligible ages

In most European countries, breast cancer screening is offered to women between the ages of 50 and 69.[3] Some countries, including the Netherlands, also offer screening for the ages 70 to 74.[3] In recent years, more research has been performed on the effectiveness of already starting screening before the age of 50. In the UK age trial, women who were invited for annual screening between the age of 40 and 48 were found to have a relative reduction in breast cancer mortality of 25% at age 50 compared to women who were not invited.[23] However, no significant reduction in mortality was found when using data with longer follow-up. The International Agency for Research on Cancer (IARC) reported in 2015 that they found the evidence for screening in women between the ages of 40 and 49 to be limited, although, a subgroup thought the evidence was sufficient for ages 45-49.[24] In the meantime, more research has been published[23,25,26] and in 2021 the European Commission Initiative on Breast Cancer (ECIBC) recommended with moderate certainty to screen women aged 45-49 every two or three years with mammography.[27] For the age group 40 to 44, the ECIBC suggests not to implement mammography screening, because of the limited amount of evidence for this group.

Personalised invitations

Currently, screening invitations in the Netherlands are the same for everyone invited. Not only in breast cancer screening, but also in cervical and colorectal cancer screening; all invitees receive the same invitation to participate in screening. However, it might be beneficial to personalise these invitations according to the amount of previous invitations, previous participation, and/or previous screening outcome. In **chapter 4** we found that women with a history of FP results have a higher TP and interval cancer rate than women with TN results, but also their participation rate is lower. Informing the women with a FP result that they have an increased risk gives them more awareness and potentially increases their participation rate. However, more research on this subject is needed to investigate the actual impact of providing personal risk information on awareness, participation, and anxiety. Furthermore, personalising information based on health literacy can contribute to the understanding of women and their knowledge on the impact of participation in the screening programme. Research on colorectal cancer screening showed that invitees with low health literacy had problems in accessing, comprehending and applying the standard information materials provided with the screening invitation which limited them in making an informed decision about participation.[28] In addition, also informed decision making in invitees with adequate health literacy was suboptimal.[29] By tailoring information on health literacy, the information can be made understandable for people with low health literacy without cutting information out that is relevant for the decision making of people with higher health literacy. However, it may be a challenge to determine the level of health literacy before sending out the invitation with the accompanying information. A solution

could be a computer-based decision aid which was found to be effective and acceptable among individuals with adequate and low health literacy in colorectal cancer screening.[30]

Risk stratification in screening

A hot topic in cancer screening research is personalising screening by applying risk stratification. By applying risk stratification, screening protocols take into account the risk of specific subgroups in the population. In breast cancer screening, stratification in subgroups can be based on genetic risk factors, breast density, family history (without genetic risk factors), and/or behavioural risk factors.

Stratified screening programmes already exist for women with well-known breast cancer mutations BRCA1/2, ATM, CHEK2, and PALB2.[31] However, genetic testing for these mutations is only done in women of whom a family member with cancer is known to have the mutation. Furthermore, these mutations explain approximately 20% of the familial risk.[32] In addition to these mutations, combinations of multiple single nucleotide polymorphisms (SNPs) together can result in an increased risk.[33,34] These SNPs can be combined into a polygenic risk score (PRS) which can be used to stratify subgroups in screening. Modelling studies found that using PRS for risk stratification can be beneficial.[35] At the moment, several ongoing trials are investigating risk stratification based on PRS (among others) in practise.[36,37] However, trials like these take time and results are only expected in a few years. Furthermore, results on long-term outcomes like breast cancer mortality reduction and overdiagnosis take even longer. Though, with proper assumptions, modelling can predict long term effects using short term trial results.

Furthermore, studies have been performed on stratified screening for women with a high mammographic breast density, because a high breast density was shown to increase breast cancer risk, while it reduces mammography sensitivity.[38-40] An example is the DENSE trial in which women with extremely dense breasts were invited for MRI screening on top of the regular mammography screening.[41] They found that MRI screening in combination with mammography in this population resulted in a strong reduction in interval cancer diagnosis, but also an increase in false-positive results. Cost-effectiveness analyses showed that MRI screening for women with extremely dense breast every three or four years was cost effective.[42] In addition, capacity investigation in Dutch hospitals and diagnostic centres showed sufficient capacity to perform MRI screening in women with extreme dense breasts every four years.[43] Recently the European Society of Breast Imaging (EUSOBI) recommended to implement MRI screening for women with extremely dense breasts.[44] At the moment, the ECIBC suggests not to implement tailored screening with MRI for women with high breast density.[45] However, they mention that this is a conditional recommendations with very low certainty of the evidence. Furthermore, they also suggest

not to use automated breast ultrasound system (ABUS) or hand-held ultrasound (HHUS) for this group.[45] They do, however, suggest using digital breast tomosynthesis (DBT) in screening for women with high mammographic breast density detected in previous screening exams.[45] Though, still no screening programme adopted tailored screening for women with extremely dense breasts yet.

Before screening organisations implement risk stratified screening, some barriers still need to be overcome. In general, the vast majority of women indicated to be positive about knowing their risk and having a tailored screening protocol based on this, however, there might be some challenges in offering low-risk women a less intensive programme.[46,47] Also, in the case of genetic risk stratification, DNA samples need to be collected in order to determine the PRS which requires consideration of legal and ethical aspects before implementation can be considered.

Imaging modalities

Currently, the standard imaging technique used for breast cancer screening is digital mammography. Over time, different imaging techniques have been developed that may improve screening.

DBT has been proposed as imaging technique to replace digital mammography in breast cancer screening. Where digital mammography creates 2D images of the breasts, DBT can create a pseudo-3D image. DBT is already used in clinical settings and in some screening centres in the USA and some regions in Europe; however some uncertainty remains around its performance in screening.[48-51] Recent meta-analyses found that with DBT the detection rate increased compared to digital mammography, although the effect of DBT on interval cancers remained unclear.[53-53] Therefore, most policy makers wait with a decision on implementing DBT for screening on more evidence. However, the ECIBC finds the evidence, even though of low certainty, strong enough to suggest using either DBT or digital mammography as imaging modality for breast cancer screening.[54]

As mentioned before, MRI can also be used for imaging of the breast. However, MRI is too costly, immobile, and time consuming to use for all women eligible for screening. All though, in a small population of high risk women screening with MRI can be worthwhile. However, previous research found that screening with MRI results in more false-positive referrals and is expected to lead to more overdiagnosis than mammography.[55,56] At the moment, all diagnosed breast cancers are treated, so every overdiagnosis directly leads to overtreatment which is unwanted. Overdiagnosis in breast cancer is thought to be mostly the case in women diagnosed with DCIS. Therefore, the LORD trial is exploring the safety of active surveillance in women with asymptomatic, screen-detected, pure low-grade DCIS

compared to standard treatment.[57] If it is safe to give these women active surveillance instead of direct treatment, overdiagnosis of these tumours will be less of a burden because it does not lead to overtreatment.

Furthermore, contrast enhanced mammography (CEM) is a relatively new imaging technique which uses iodinated contrast material in combination with mammography. In a diagnostic setting, CEM was found to perform similar as MRI, but was less time consuming and less costly.[58] However, so far, CEM was only studied in diagnostic settings and for screening of high risk women. At the moment three trials are investigating CEM in a screening setting for women with dense breasts.[59-61] Also cost-effectiveness of CEM in screening is still unknown.

Another upcoming technique that can potentially improve breast cancer screening is artificial intelligence (AI). Using AI, algorithms are trained to read breast images and select which women need to be referred for follow-up. AI can be used for all screening modalities, as long as there are enough images available to train and validate the algorithm. A well trained mammography algorithm was found to be able to replace the second reader leading to an increase in specificity while sensitivity remained equal.[62] On top of that, using an algorithm to replace the second reader was estimated to lead to a reduction of workload of 40 to 70%.[62,63] So AI may not only improve screening performance, but is also likely to reduce the required capacity of mainly radiologists. However, a meta-analysis concluded that AI is not yet ready to be implemented in practise, because the results are not sufficiently specific and promising results in smaller studies are not replicated in larger studies.[64] Yet, the capital region of Denmark did implement the Transpara AI algorithm as part of their screening programme since November 2021 which resulted in a 29% reduction in reader workload and a non-significant lower recall rate.[65] It is, however, still unknown if the lower recall rate affected the detection rate. Moreover, existing algorithms need to be improved and studied in practise to prove their effectiveness before they can be implemented in screening programmes on a larger scale.

Combination of cancer screening programmes

Many countries offer their citizens multiple screening programmes and most, if not all, of the cancer screening programmes have an overlap in the age groups that are eligible for screening. In **chapter 3** we studied concurrent participation to breast, cervical, and colorectal cancer screening for the overlapping eligible ages in the Netherlands. We found that the timing of the three screening invitations (<3 months, 3-6 months, or >6 months apart) did not have a relevant effect on concurrent participation. Therefore, the timing of the three programmes does not have to be adjusted to each other. However, combining multiple screening invitations may have other benefits that can make it interesting to

consider (e.g. potentially time saving, possibly more awareness, more sustainable). On the other hand, it can also create harms that were not visible in the previous results (e.g. more stress). In addition, receiving a combined invitation instead of separate invitations close in time may still lead to a lower participation rate, for example due to missing information or misunderstanding. Furthermore, in the Netherlands the three existing cancer screening programmes have different screening intervals which would need to be adjusted to allow for screening examination to be performed at the same appointment.

Another option could be a combination of screening tests during one appointment. Currently, Dutch screening centres are not designed to combine multiple screening tests, because breast screening takes place in mobile units and cervical screening at GP offices and both don't have place to accommodate each other. Furthermore, colorectal cancer screening uses a home sampling test for which participants don't have to make an appointment. However, in the future a change of screening tests or additions of new screening programmes or tests may allow for better combination of tests during one appointment. For example, if lung cancer screening is implemented, there might be a possibility to screen people eligible for both lung and breast cancer screening during one appointment since both screening tests use imaging on the upper part the body. However, lung cancer screening research points towards chest-CTs that need to be made in a hospital setting.[66] Since breast cancer screening is performed in special units, combining the two screening tests in the hospital will probably not be beneficial. An example of a new screening test that might allow for a combination of tests is testing with liquid biopsies. Liquid biopsies are fluid samples that can contain biomarkers like circulating tumour cells, cell-free DNA, microRNA, microvesicles or platelets which all contain tumour-derived information.[67] They can be samples of blood, urine, saliva, sweat, nipple aspirate fluid, tears, and breath.[68] An advantage of liquid biopsies is that they are collected 'non-invasively' and can potentially be used to screen for multiple cancers at the same time. However, up till now, studies on liquid biopsies in breast cancer screening did not show sufficient sensitivity to detect circulating tumour DNA.[67] Also in women referred to the hospital with suspicion of breast cancer, liquid biopsies were not able to discriminate between women with and without breast cancer.[69]

Quality of life

Next to the reduction in mortality, an increase in health related quality of life is also an important aim of cancer screening programmes. Over time, cost-effectiveness analyses (CEAs) on screening strategies increasingly include quality adjusted life years (QALYs) to evaluate quality of life. However, in order to do this, utility values are needed for the normative population, screening and follow-up stages, and disease health states. However, utility values for breast cancer CEAs are heterogeneous and often based on expert opinion

or 'what if?' situations valued by the general public.[70] In **chapter 8 and 9** of this thesis we provided data and experience based utility values for the normative population and during different stages of breast cancer treatment. **Chapter 9** also showed that variation in the utility values used in normative, screening and follow-up, and treatment health states can lead to differences in QALYs. Therefore, it is important to have precise and reliable utility values for the normative population, breast cancer screening, and breast cancer stages. However, there is still uncertainty around the quality of life people experience during different steps of the screening programme. Furthermore, there are large variations in utility values found in different studies. A large part of this variation is caused by the use of different health utility estimation methods.[70] In order to reduce this variation, it would be good to standardise the methods on estimating utility values to be used in CEAs.

FINAL CONCLUSIONS

The organised population-based breast cancer screening programme in the Netherlands is effective in preventing many women to die from the disease and in improving quality of life. In addition, it has shown to maintain a relatively high level of informed participation.

However, there are still opportunities to improve the programme, for example by improving communication to the invitees, optimising the screening modality, interval, and eligible population, and introducing risk-based screening strategies. Implementation of these improvements will lead to an advanced breast cancer screening programme with more informed choices, a higher quality of life in women and a larger breast cancer mortality reduction while harms like false-positives can be reduced without increasing costs or requiring more personnel.

This thesis resulted in the following findings about breast cancer screening in the Netherlands:

- Breast cancer screening is preventing more than 21,000 breast cancer deaths in Europe each year of which approximately 1,300 in the Netherlands. These mortality reductions can increase if the participation rates increase.
- The participation rate of the Dutch breast cancer screening programme slowly decreased from 82% in 2008 to 76% in 2019. However, the participation rate is still relatively high compared to participation in breast cancer screening programmes in other countries and compared to participation in other cancer screening programmes in the Netherlands.
- Around age 55 and 60, 54% of the women participate in the Dutch breast, cervical, and colorectal cancer screening programmes, while 12% do not participate in any of these three.
- When participating in seven screening examinations of the Dutch breast cancer screening programme, the cumulative risk of having a TP result is 3.7% and of a FP result is 9.1%. After eleven examinations, this increases to 7.1% and 13.5%, respectively.
- Women with a history of FP results less often participate in next rounds, but more often had TP results, interval cancers and additional FP results when participating in later screening rounds.
- After a disruption in cancer screening, it is best to catch up all missed screening tests while continuing the original planning if capacity allows for this. The best alternative is to restart screening where the planning was disrupted and to increase the stopping age with the length of the disruption. By doing this, everyone will be able to be invited for the same amount of screening tests during their life as without the disruption.

- From a cost-effectiveness point of view, triennial screening for the ages 44 to 71 or 74 is more beneficial than the current biennial screening programme for the ages 50 to 74, because the triennial strategies yield more QALYs and have lower costs. When capacity allows, screening biennially for a wider age range can also be considered.
- Women who read the information leaflet have a higher positive attitude towards breast cancer screening and have more knowledge about the screening than women who do not read the leaflet. This difference is largest for women who are invited for breast cancer for the first time.
- There is no correlation between implicit attitude towards breast cancer screening and participation in the screening programme.
- Women in the Netherlands score their health related quality of life a 9.1 on average with highest scores in younger women which slowly decrease with increasing age.
- Assuming perfect health in a normative population leads to an overestimation of QALYs gained.
- Varying utilities associated with breast cancer treatment and breast cancer screening and follow-up has a limited effect on QALYs which results in robust optimal strategies in cost-effectiveness analyses.

RECOMMENDATIONS

- Investigate the effects and acceptability of changing the screening strategy into triennial screening, while starting screening at a younger age, for example by using data from the period in which the interval was increased due to personnel shortages. Furthermore, triennial screening should be investigated in combination with more intensive screening strategies or other modalities for subgroups at higher risk.
- Include information about the FP/TP ratio and cumulative screening risks specific for the Dutch breast cancer screening programme in the information folder provided with the screening invitation in a way that is understandable for everyone.
- Provide personalised information with screening invitations and in result letters to include information on personalised breast cancer risk and influencing factors like history of FP results. In addition, investigate the use of different communication tools to improve reading and understanding.
- Use gender and age specific normative utility values based on data from a comparable population to avoid overestimation of QALYs gained.
- Continue to evaluate the effectiveness of the established screening programme, because a changing context can lead to a change in the optimal strategy. Simultaneously, investigate the value of new screening modalities, risk stratifying strategies, and the added value of AI in this to further improve the screening programme.

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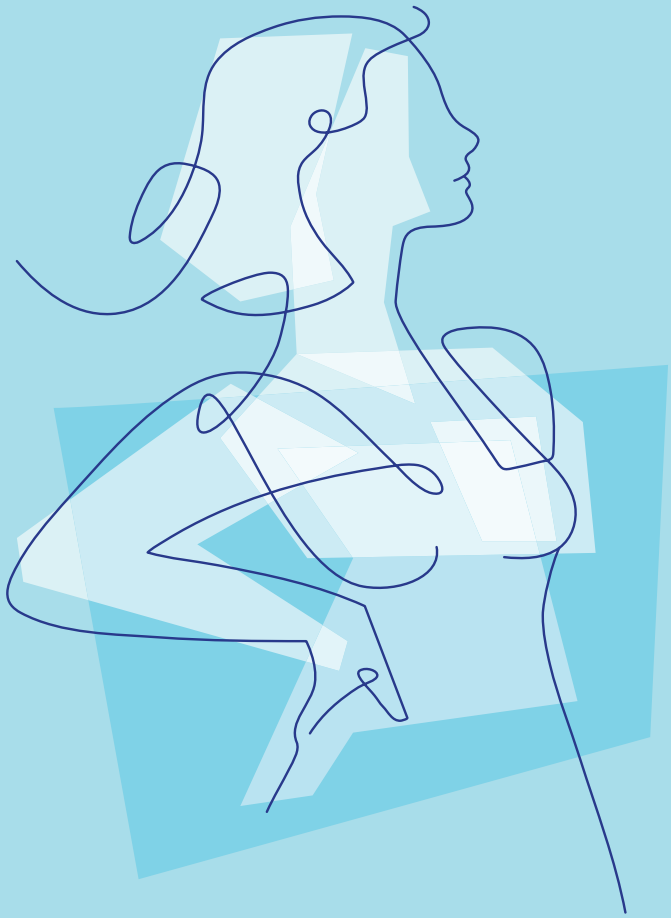


Summary

SUMMARY

With an estimated 2.1 million new cases per year, breast cancer is the most prevalent cancer among women worldwide. Therefore, it is a major health concern. Over time, the incidence of breast cancer has increased, due to an aging population and an increase in the prevalence of risk factors. At the moment, almost all breast cancer patients receive treatment which can consist of neo-adjuvant treatment, surgery, radiation, and/or adjuvant therapy. Over time, treatment options have improved which led to a decrease in mortality and an improvement of quality of life. At the moment, the 10-year survival is 93% for early breast cancer, 62% for locally advanced cancers, and 9% for metastatic breast cancer in Dutch women.

Next to improvements in treatment, the mortality reduction is also caused by the introduction of breast cancer screening. The aim of breast cancer screening is to detect and treat early stage breast cancer in asymptomatic women to decrease the mortality from the disease and allow for less invasive treatment thereby increasing life expectancy and quality of life. In the Netherlands, women between the age of 50 and 74 are invited for digital mammography every two years. Next to benefits like a reduction in mortality and an increase in quality of life, breast cancer screening also leads to harm like overdiagnosis and false-positive results. In order to monitor the balance between benefits and harms, the screening programme is evaluated continuously.

This thesis aimed to contribute to the evaluation of the effectiveness of the Dutch breast cancer screening programme and to investigate potential improvements to the programme. In addition, this thesis investigated the perspectives of the women eligible for breast cancer screening.

Part 1: Effectiveness of breast cancer screening

In chapter 2 of this thesis, we found that throughout Europe, an estimated 21,680 breast cancer deaths were prevented annually due to screening women between the age of 50 and 69. Furthermore, it was estimated that an additional 12,434 can be prevented with a 100% examination rate. When looking specifically at the Netherlands, this resulted in approximately 1400 breast cancer deaths prevented due to screening in 2015, and potentially 350 more if the participation would increase to 100%. Because the Dutch breast cancer screening programme also invites women in the age category 70-74, potentially even more breast cancer deaths are being prevented.

In chapter 3, we examined concurrent participation across the breast, cervical, and colorectal cancer screening programmes. We found that 54% of women aged 55 and

60 participated in all three screening programmes, 22% in two, 12% in one, and 12% in none of them. Internationally seen, this is quite high, suggesting that in general women in the Netherlands have a positive view towards participating in all three programmes. Furthermore, this study found that women living in areas with higher population density were less likely and women in higher SES groups were more likely to participate in more screening programmes.

Chapter 4 describes the effects of participating in breast cancer screening for multiple examinations over time. We found that, when participating in seven screening examinations, the cumulative risk of having a false positive (FP) result was 9.1% and of having a screen-detected breast cancer was 3.7% (true positive (TP)). After extrapolating this to eleven examinations, this increased to 13.5% and 7.1%, respectively. Furthermore, we found that women who had a FP result participated less often in the next screening round than women who had a true negative result, while the incidence rate of FP, TP, and interval cancers was higher among women who had a history of FP results.

During the first wave of Coronavirus disease (COVID-19) and its accompanying lockdown in 2020, many countries disrupted their cancer screening programmes. This led to a one-time elongation in the screening interval. Chapter 5 of this thesis described that the effects of a six month screening disruption would have a small effect on cervical cancer incidence and mortality, but a more substantial effect on breast and colorectal cancer mortality. However, this effect could be avoided almost completely by catching up all missed screening tests on top of continuing the original schedule when restarting screening compared to undisrupted screening. This restart strategy, however, would require a doubling in capacity during the six months after screening was restarted. When this is not possible due to limited capacity, the loss in prevented mortality can be reduced by restarting screening where the schedule was disrupted and simultaneously increasing the stopping age with six months, so no last round would be omitted. By doing so, additional mortality could be limited to 1.6, 0.1, and 2.0 additional breast, cervical, and colorectal cancer deaths per 100,000 eligible individuals, respectively.

In chapter 6, the cost-effectiveness of 920 different breast cancer screening strategies was analysed using the MISCAN-Breast model. We found that, using a conservative willingness to pay threshold of €20,000 per quality adjusted life year (QALY) gained, biennial screening for ages 40 to 76 would be most optimal resulting in 33% more breast cancer deaths prevented and 46% more QALYs gained than the current strategy. However, this strategy also resulted in 25% more overdiagnoses and 90% more FP results, and required a 34% higher screening capacity than the current strategy. The current Dutch strategy (biennial screening for the ages 50 to 74) was close to, but not on the efficiency frontier. This

means that there were other strategies that yielded (slightly) more effect while costing less money. These alternatives were triennial screening for the ages 44 to 71 or 44 to 74 which resulted in 5% and 7% more QALYs gained, respectively, while costs were 5% and 1% lower and the required capacity was 17% and 22% lower. Since a few years, the Dutch breast cancer screening programme has been dealing with a capacity restraint due to a shortage in imaging personnel. Given this constraint in screening capacity, expanding the screening population to a wider age range, without extending the interval is not an option at the moment. As an alternative, the triennial screening strategies for ages 44 to 71 or 74 can be considered because they yield more QALYs, less costs, and less capacity than the current biennial strategy.

Part 2: Perspectives of the women

Besides effectiveness, the success of an intervention or programme is determined by how its target population feels about it. In part two of this thesis, the perspectives of the women who are eligible for screening were investigated by looking at attitudes, knowledge, informed choice, and quality of life.

Attitudes can be subdivided into explicit and implicit attitudes. Explicit attitudes are deliberate and present at the conscious level, while implicit attitudes are unconscious and influence behaviour without people's awareness. In chapter 7 we found that women who were asked to read the official screening information leaflet slightly more often had more knowledge and had a positive explicit attitude towards breast cancer screening than the women who did not receive the leaflet. The increase in knowledge was most pronounced in women who were about to be invited for their first examination of breast cancer screening. No differences were found in implicit attitude, intention to participate, actual participation, and informed choice. In addition, we found that implicit associations were not correlated with explicit attitude or attendance. Explicit attitudes were correlated with attendance, but only moderately. This means that women do not make a decision about screening participation based on their implicit attitude. Their decision is based on their explicit attitude, but this does not completely explain participation behaviour, so other factors are involved as well.

In chapter 8 we measured the quality of life of a large cohort of women living in the Netherlands between the ages of 18 and 90 years old. We found an average normative utility of 0.91 for Dutch women and a declining trend with increasing age. Compared to other normative utility scores of female populations, our mean utilities were consistently higher except for women under 35 years of age.

In chapter 9 we found that, compared to normative utilities, women had lower utilities right after a breast cancer diagnosis, which decreased more until twelve months after surgery. However, differences in patterns were observed between age groups and types of treatment. In cost-effectiveness analyses with different utility sets we found that using 'perfect health' for normative utilities led to overestimation of the amount of QALYs gained by screening compared to the gender and age specific utilities from chapter 8. When using different breast cancer utility sets, we found that differences in QALYs gained were only small and mainly visible when comparing biennial and annual screening strategies. Sensitivity analyses on screening and follow-up utilities showed that variation among these utilities did not lead to noteworthy differences in QALYs gained. Despite the differences in normative, treatment and screening and follow-up utility sets, the strategies on the efficiency frontier and the optimal strategy remained quite robust.

Conclusions

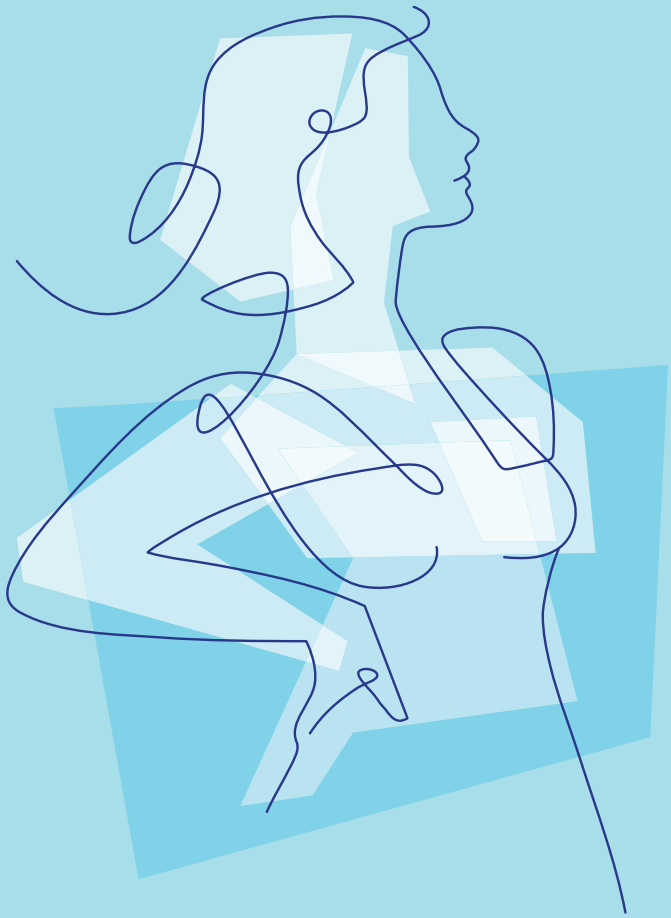
This thesis resulted in the following conclusions about breast cancer screening in the Netherlands:

- Breast cancer screening is preventing more than 21,000 breast cancer deaths in Europe each year of which approximately 1,300 in the Netherlands. These mortality reductions can increase if the participation rates increase.
- The participation rate of the Dutch breast cancer screening programme slowly decreased from 82% in 2008 to 76% in 2019. However, the participation rate is still relatively high compared to participation in breast cancer screening programmes in other countries and compared to participation in other cancer screening programmes in the Netherlands.
- Around age 55 and 60, 54% of the women participate in the Dutch breast, cervical, and colorectal cancer screening programmes, while 12% do not participate in any of these three.
- When participating in seven screening examinations of the Dutch breast cancer screening programme, the cumulative risk of having a TP result is 3.7% and of a FP result is 9.1%. After eleven examinations, this increases to 7.1% and 13.5%, respectively.
- Women with a history of FP results less often participate in next rounds, but more often had TP results, interval cancers and additional FP results when participating in later screening rounds.
- After a disruption in cancer screening, it is best to catch up all missed screening tests while continuing the original planning if capacity allows for this. The best alternative is to restart screening where the planning was disrupted and to increase the stopping age with the length of the disruption. By doing this, everyone will be able to be invited for the same amount of screening tests during their life as without the disruption.

- From a cost-effectiveness point of view, triennial screening for the ages 44 to 71 or 74 is more beneficial than the current biennial screening programme for the ages 50 to 74, because the triennial strategies yield more QALYs and have lower costs. When capacity allows, screening biennially for a wider age range can also be considered.
- Women who read the information leaflet have a higher positive attitude towards breast cancer screening and have more knowledge about the screening than women who do not read the leaflet. This difference is largest for women who are invited for breast cancer for the first time.
- There is no correlation between implicit attitude towards breast cancer screening and participation in the screening programme.
- Women in the Netherlands score their health related quality of life a 9.1 on average with highest scores in younger women which slowly decrease with increasing age.
- Assuming perfect health in a normative population leads to an overestimation of QALYs gained.
- Varying utilities associated with breast cancer treatment and breast cancer screening and follow-up has a limited effect on QALYs which results in robust optimal strategies in cost-effectiveness analyses.

Recommendations

- Investigate the effects and acceptability of changing the screening strategy into triennial screening, while starting screening at a younger age, for example by using data from the period in which the interval was increased due to personnel shortages. Furthermore, triennial screening should be investigated in combination with more intensive screening strategies or other modalities for subgroups at higher risk.
- Include information about the FP/TP ratio and cumulative screening risks specific for the Dutch breast cancer screening programme in the information folder provided with the screening invitation in a way that is understandable for everyone.
- Provide personalised information with screening invitations and in result letters to include information on personalised breast cancer risk and influencing factors like history of FP results. In addition, investigate the use of different communication tools to improve reading and understanding.
- Use gender and age specific normative utility values based on data from a comparable population to avoid overestimation of QALYs gained.
- Continue to evaluate the effectiveness of the established screening programme, because a changing context can lead to a change in the optimal strategy. Simultaneously, investigate the value of new screening modalities, risk stratifying strategies, and the added value of AI in this to further improve the screening programme.



Samenvatting

SAMENVATTING

Borstkanker is de meest voorkomende kankersoort met 2,1 miljoen nieuwe diagnoses per jaar wereldwijd. Daarom is het een groot gezondheidsprobleem. De laatste decennia is de incidentie van borstkanker toegenomen, veroorzaakt door vergrijzing en een toename van risicofactoren. Momenteel ontvangen bijna alle borstkankerpatiënten een behandeling die bestaat uit neo-adjuvante therapie, chirurgie, bestraling en/of adjuvante therapie. De behandeling van borstkanker is de afgelopen jaren verbeterd waardoor de borstkankersterfte is afgenomen en de kwaliteit van leven is toegenomen. Momenteel is in Nederland de 10-jaars overleving 93% voor borstkanker in een vroeg stadium, 62% voor borstkanker in een later stadium en 9% voor uitgezaaide borstkanker.

De afgenomen sterfte is niet alleen een gevolg van de verbeterde behandel opties. De introductie van het bevolkingsonderzoek borstkanker heeft hier ook aan bijgedragen. Het doel van het bevolkingsonderzoek is om borstkanker in een vroeg stadium te vinden en behandelen, nog voor symptomen optreden, om zo de borstkankersterfte te verlagen en te kunnen behandelen met minder invasieve behandelopties, wat een positief effect heeft op de levensverwachting en kwaliteit van leven. In Nederland worden vrouwen tussen de 50 en 74 jaar elke twee jaar uitgenodigd voor een digitaal mammogram. Naast voordelen, heeft het bevolkingsonderzoek ook nadelen zoals overdiagnose en fout-positieve (FP) resultaten. Om te zorgen dat de voordelen en nadelen in balans zijn, wordt het bevolkingsonderzoek continu geëvalueerd.

Dit proefschrift heeft als doel om bij te dragen aan de evaluatie van de effectiviteit van het Nederlandse bevolkingsonderzoek borstkanker en om potentiële verbeteringen te onderzoeken. Daarnaast heeft die proefschrift onderzocht wat de opvattingen zijn van de vrouwen die uitgenodigd worden voor het bevolkingsonderzoek.

Deel 1: Effectiviteit van het bevolkingsonderzoek borstkanker

In hoofdstuk 2 van dit proefschrift vonden we dat in heel Europa elk jaar waarschijnlijk 21.680 borstkankersterfgevallen zijn voorkomen door bevolkingsonderzoeken naar borstkanker voor vrouwen tussen de 50 en 69 jaar. Daarnaast werd er geschat dat er jaarlijks 12.343 extra sterfgevallen voorkomen kunnen worden wanneer 100% van alle Europese vrouwen deelneemt aan het bevolkingsonderzoek. In Nederland werd er geschat dat er reeds ongeveer 1.400 borstkankersterfgevallen werden voorkomen en er mogelijk 350 extra voorkomen konden worden bij 100% deelname aan het bevolkingsonderzoek. In deze studie werd alleen gekeken naar de leeftijdsgroep 50 tot 69, maar omdat in Nederland vrouwen worden uitgenodigd tot leeftijd 74 wordt er mogelijk al meer borstkankersterfgevallen voorkomen.

In hoofdstuk 3 werd onderzocht in hoeverre de deelname aan de bevolkingsonderzoeken naar borst-, baarmoederhals- en dikke darmkanker overlappen. We vonden dat 54% van de vrouwen op leeftijd 55 of 60 deelnam aan alle drie de bevolkingsonderzoeken, 22% nam deel aan twee, 12% aan één en 12% nam deel aan geen enkel bevolkingsonderzoek. Vergeleken met studies uit andere landen, namen relatief veel vrouwen deel aan de bevolkingsonderzoeken. Dit geeft de indicatie dat vrouwen in Nederland over het algemeen positief tegenover deelname aan de drie bevolkingsonderzoeken aankijken. Daarnaast vond deze studie dat vrouwen woonachtig in steden met een hoge populatiedichtheid minder vaak deelnamen aan meerdere bevolkingsonderzoeken en vrouwen met een hogere socio-economische status vaker deelnamen aan meerdere bevolkingsonderzoeken.

Hoofdstuk 4 beschrijft de effecten van deelname aan het bevolkingsonderzoek borstkanker voor meerdere onderzoeken door de tijd. We vonden dat wanneer vrouwen zeven keer deelnamen aan het bevolkingsonderzoek, de cumulatieve kans op een FP uitslag 9,1% was en de cumulatieve kans op het vinden van een borstkanker 3,7% was (terecht-positief (TP)). Na extrapolatie voor elf deelnames was dit toegenomen tot 13,5% voor een FP uitslag en 7,1% voor een TP uitslag. Daarnaast vonden we dat vrouwen die eerder een FP uitslag hadden, daarna minder vaak deelnamen aan een volgend onderzoek dan vrouwen die een terecht negatieve uitslag hadden. Terwijl bij vrouwen met een FP uitslag de incidentie van FP resultaten, TP resultaten en intervalkankers in latere onderzoeken hoger was.

Gedurende de eerste golf van COVID-19 en de bijbehorende lockdown in 2020 werden de bevolkingsonderzoeken voor kanker stilgelegd in vele landen. Hierdoor werden de intervallen tussen twee onderzoeksrondes in het bevolkingsonderzoek eenmalig verlengd. In hoofdstuk 5 van dit proefschrift beschreven we dat de effecten van een onderbreking van zes maanden slechts een klein effect hadden op de incidentie en mortaliteit van baarmoederhalskanker, maar een substantieel effect op de mortaliteit van borst- en dikke darmkanker vergeleken met een situatie zonder onderbreking. Dit effect kon grotendeels voorkomen worden door, op het moment dat de bevolkingsonderzoeken weer van start konden, alle gemiste onderzoeken in te halen en tegelijkertijd verder te gaan met de originele planning. Echter, hiervoor was een verdubbeling van de capaciteit nodig gedurende de zes maanden na de herstart. Mocht dit niet mogelijk zijn, dan kon het effect op mortaliteit beperkt worden door bij herstart verder te gaan waar gestopt was en daarbij de eindleeftijd van de doelgroep te verhogen met zes maanden zodat niemand het laatste onderzoek zou missen. Hierdoor kon de extra mortaliteit beperkt blijven tot 1,6, 0,1 en 2,0 extra borst-, baarmoederhals- en dikke darmkanker sterfgevallen per 100.000 uitgenodigde personen, respectievelijk.

In hoofdstuk 6 werd de kosteneffectiviteit van 920 verschillende strategieën voor het bevolkingsonderzoek borstkanker onderzocht aan de hand van het MISCAN-Borst model. Met een grens van bereidheid tot betaling (WTP) van €20.000 per voor kwaliteit van leven gecorrigeerd levensjaar (QALY) was een 2-jaarlijks bevolkingsonderzoek voor vrouwen tussen de 40 en 76 het meest optimaal. Bij deze strategie werden 33% meer borstkanker sterfgevallen voorkomen en 46% meer QALYs gewonnen dan met de huidige strategie (2-jaarlijks voor de leeftijden 50-74). De huidige strategie in Nederland was dicht bij de effectiviteitsgrens, maar lag er net onder. Dit betekent dat er andere strategieën waren die effectiever waren met minder kosten. Deze strategieën waren 3-jaarlijks testen voor leeftijden 44 tot 71 of leeftijden 44 tot 74. Deze strategieën wonnen respectievelijk 5% en 7% meer QALYs, kostten 5% en 1% minder en hadden een benodigde capaciteit die 17% en 22% lager lag dan de huidige strategie. Sinds een aantal jaren heeft het Nederlandse bevolkingsonderzoek borstkanker een capaciteitsprobleem vanwege een tekort aan radiologisch laboranten. Door dit tekort is het momenteel niet mogelijk om de leeftijdsrange te verbreden zonder het interval te verlengen. Als alternatief is 3-jaarlijks testen voor de leeftijdsgroep 44 tot 71 of 44 tot 74 een optie om te overwegen vanwege het hogere aantal gewonnen QALYs, de lagere kosten en de lagere benodigde capaciteit vergeleken met de huidige strategie.

Deel 2: Opvattingen van de vrouwen

Het succes van een interventie of bevolkingsonderzoek wordt niet alle bepaald door de effectiviteit, maar ook door de opvattingen van de doelgroep. In het tweede deel van dit proefschrift werden de opvattingen van de uitgenodigde vrouwen voor het bevolkingsonderzoek borstkanker bestudeerd door te kijken naar attitude, kennis, geïnformeerde keuze en kwaliteit van leven.

Attitudes kunnen onderverdeeld worden in expliciete en impliciete attitudes. Expliciete attitudes zijn weloverwogen en worden bewust gemaakt, terwijl impliciete attitudes onbewust een effect hebben op iemands gedrag. In hoofdstuk 7 vonden we dat vrouwen die gevraagd werden de officiële informatiefolder van het bevolkingsonderzoek borstkanker te lezen meer kennis hadden over het bevolkingsonderzoek en vaker een positieve expliciete attitude hadden over het bevolkingsonderzoek dan vrouwen die de folder niet hadden gezien. De toename in kennis was het grootst in de groep vrouwen die nog niet eerder waren uitgenodigd voor het bevolkingsonderzoek borstkanker. Er werd geen verschil gevonden tussen de groepen op het gebied van impliciete attitude, intentie tot deelname, werkelijke deelname en geïnformeerde keuze. Daarnaast werd geen correlatie gevonden tussen de impliciete attitude en de expliciete attitude of deelname. De expliciete attitude was wel gecorreleerd met deelname, maar slechts matig. Dit betekent dat de keuze voor deelname aan het bevolkingsonderzoek borstkanker niet beïnvloed

werd door de impliciete attitude. Deze keuze is wel beïnvloed door de expliciete attitude, maar dit verklaart niet volledig het deelname gedrag, dus er zijn nog andere factoren bij betrokken.

In hoofdstuk 8 hebben we de kwaliteit van leven gemeten in een groot cohort vrouwen woonachtig in Nederland in de leeftijd tussen 18 en 90 jaar oud. Hierbij vonden we een gemiddelde normatieve utiliteit van 0,91 voor Nederlandse vrouwen die het hoogst was onder jonge vrouwen en afnam met toenemende leeftijd. Vergeleken met andere normatieve utiliteitswaardes in vrouwelijke populaties waren onze waardes consistent hoger, behalve voor de groep onder de 35 jaar oud.

In hoofdstuk 9 vonden we dat, vergeleken met de normatieve utiliteiten, vrouwen lagere utiliteiten hadden vlak nadat zij de diagnose borstkanker ontvingen, wat nog verder af nam tot twaalf maanden na chirurgie. Hierbij waren verschillen zichtbaar tussen leeftijdsgroepen en het type behandeling die patiënten ontvingen. In kosten-effectiviteitsanalyses waarbij verschillende utiliteiten sets werden gebruikt vonden we dat het gebruik van 'perfecte gezondheid' als normatieve utiliteit leidde tot overschatting van de gewonnen QALYs vergeleken met geslachts- en leeftijdsspecifieke utiliteiten uit hoofdstuk 8. Verschillen in utiliteiten voor de behandeling van borstkanker leidde slechts tot kleine verschillen in gewonnen QALYs die vooral zichtbaar waren bij de vergelijking van 2-jaarlijkse en jaarlijkse strategieën. Sensitiviteitsanalyses op utiliteiten voor het bevolkingsonderzoek en diagnostische testen liet zien dat variaties in de utiliteiten geen noemenswaardig effect had op de gewonnen QALYs. Ondanks de verschillen in normatieve, behandeling en bevolkingsonderzoek utiliteiten waren de strategieën op de effectiviteitsgrens en de optimale strategie tamelijk robuust.

Conclusies

Dit proefschrift heeft geresulteerd in de volgende conclusies over het bevolkingsonderzoek borstkanker in Nederland:

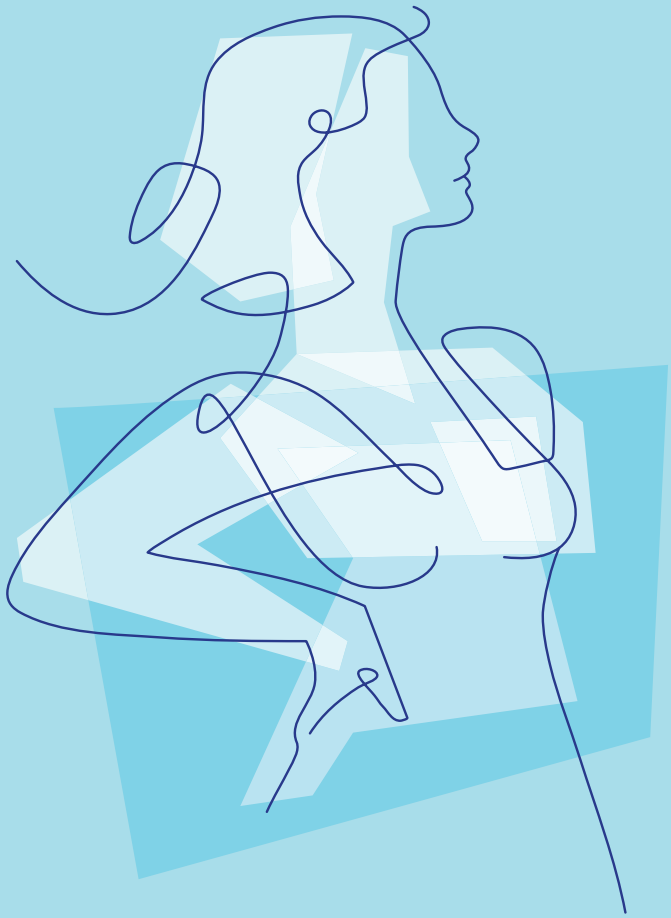
- Bevolkingsonderzoeken naar borstkanker in Europa voorkomen meer dan 21.000 borstkankersterfgevallen per jaar waarvan ongeveer 1.300 in Nederland. De aantallen voorkomen sterfgevallen kunnen toenemen als de deelnamegraad stijgt.
- De deelnamegraad van het Nederlandse bevolkingsonderzoek borstkanker nam de afgelopen jaren af van 82% in 2008 tot 76% in 2019. Desondanks is de deelnamegraad nog relatief hoog is vergeleken met ander landen en vergeleken met de andere bevolkingsonderzoeken in Nederland.
- Rond leeftijd 55 en 60 neemt 54% van de vrouwen in Nederland deel aan zowel het bevolkingsonderzoek naar borst-, baarmoederhals- en dikke darmkanker terwijl 12% aan geen enkel programma deelnam.

- Wanneer vrouwen deelnemen aan zeven opvolgende onderzoeken van het bevolkingsonderzoek borstkanker is hun cumulatieve kans op een terecht positieve uitslag 3,7% en op een fout-positieve uitslag 9,1%. Na elf opvolgende onderzoeken is dit toegenomen tot 7,1% en 13,5% respectievelijk.
- Vrouwen die in het verleden een FP uitslag hebben gehad nemen in de daaropvolgende ronde minder vaak deel aan het bevolkingsonderzoek borstkanker terwijl zij vaker TP resultaten, intervalkankers en aanvullende FP resultaten ontvingen in opvolgende rondes.
- Na een onderbreking in bevolkingsonderzoeken naar kanker kan er het beste herstart worden door alle gemiste testen in te halen tijdens het vervolgen van de originele planning, als de capaciteit dit toestaat. Het beste alternatief is om te herstarten waar gestopt is en de eindleeftijd op te hogen met de lengte van de onderbreking. Hierdoor krijgt iedereen de kans het maximaal aantal testen in een leven te krijgen.
- Vanuit het perspectief van kosteneffectiviteit is een bevolkingsonderzoek borstkanker met 3-jaarlijks testen voor de leeftijden 44 tot 71 of 44 tot 74 voordeliger dan het huidige 2-jaarlijkse beleid voor leeftijden 50 tot 74, omdat de 3-jaarlijkse strategieën meer QALYs opleveren voor minder kosten. Wanneer de capaciteit het toestaat is een 2-jaarlijkse strategie voor een brede leeftijdsgroep ook het overwegen waard.
- Vrouwen die de informatiefolder lezen hebben een positievere expliciete mening en meer kennis over het bevolkingsonderzoek borstkanker dan vrouwen die de folder niet gelezen hebben. Het effect van de folder is het grootst voor de vrouwen die voor het eerst worden uitgenodigd voor het bevolkingsonderzoek.
- Er is geen correlatie tussen de impliciete mening over het bevolkingsonderzoek borstkanker en deelname hieraan.
- Vrouwen in Nederland scoren hun gezondheid gerelateerde kwaliteit van leven gemiddeld een 9,1 waarbij de scores het hoogst zijn onder de jongere vrouwen en langzaam afnemen met een toenemende leeftijd.
- De aanname van 'perfecte gezondheid' als normatieve utiliteit leidt tot overschatting van de gewonnen QALYs.
- Variëren in utiliteiten voor borstkanker behandeling, bevolkingsonderzoek en diagnose heeft een beperkt effect op QALYs en leidt tot robuuste optimale strategieën in kosteneffectiviteitsanalyses.

Aanbevelingen

- Onderzoek de effecten en de aanvaardbaarheid van een verandering van het beleid naar 3-jaarlijks terwijl er al op eerdere leeftijden gestart wordt. Bijvoorbeeld door data te gebruiken uit de periode waarin de intervallen verlengd waren door personeelstekorten. Daarnaast moet een 3-jaarlijks interval onderzocht worden in combinatie met intensiever testen of andere modaliteiten voor hoog-risico groepen.

- Includeer informatie over de FP/TP ratio en cumulatieve kansen van het Nederlandse bevolkingsonderzoek borstkanker in de informatiefolder die meegestuurd wordt met de uitnodigingsbrief op een manier die voor iedereen begrijpelijk is.
- Personaliseer de informatie in de informatiefolder en de uitslagbrief over het persoonlijke risico op borstkanker en factoren die dit beïnvloeden zoals een geschiedenis van FP resultaten. Aanvullend: onderzoek het gebruik van verschillende communicatiemiddelen om de leesbaarheid en begrijpbaarheid te verbeteren.
- Gebruik geslacht- en leeftijdsspecifieke normatieve utiliteiten gebaseerd op data van een vergelijkbare populatie om overschatting van QALYs te voorkomen.
- Continueer de evaluatie van de effectiviteit van het bestaande bevolkingsonderzoek, omdat een veranderende context kan leiden tot een verandering in optimale strategie. Onderzoek tegelijkertijd de waarde van nieuwe modaliteiten, manieren van risico-stratificatie en de toegevoegde waarde van kunstmatige intelligentie hierin om het bevolkingsonderzoek verder te verbeteren.



CURRICULUM VITAE

Lindy Kregting was born on the 21st of November in 1994 in Gendt, the Netherlands. In 2013, she graduated from secondary school at the 'atheneum' level from Over Betuwe College (OBC) Bemmel. In addition to her secondary school diploma, she also received the International Baccalaureate (IB) English Language and Literature diploma. Lindy continued her education at the Radboud University in Nijmegen where she studied Biomedical Sciences (bachelor and master). During the master programme, she focussed on epidemiological research with complementary classes on research communication. During her studies, Lindy had the opportunity to do multiple internships at the department for Health Evidence and the department for ReShape and Innovation both at Radboudumc. After graduating in 2018, Lindy started her career by working as a PhD student at the department of Public Health at Erasmus MC in Rotterdam. Her work focussed on the evaluation of the Dutch Breast cancer screening programme as part of the National Evaluation Team Breast cancer screening (NETB). In addition, her work included collaborations with colleagues on breast cancer screening in other populations and screening programmes for other cancers.

Currently, Lindy is working as a postdoctoral researcher at the department for Health Evidence at Radboudumc where she continues her research on breast cancer screening and additionally on cervical cancer screening.

LIST OF PUBLICATIONS

Publications in this thesis:

Kregting LM, van Ravesteyn NT, Spijker W, Dierks T, Aitken CA, Geuzinge HA, Korfage IJ. Effects of a leaflet on breast cancer screening knowledge, explicit attitudes, and implicit associations. Patient Education and Counseling 2020;103: 2499-507.

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Publications not in this thesis:

Sankatsing DVD, Geuzinge HA, Fracheboud J, van Ravesteyn NT, Heijnsdijk EAM, **Kregting LM,** Broeders MJM, Otten JDM, Verbeek ALM, Pijnappel RM, de Bruijn AE, de Koning HJ, Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker (LETB). Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 2004 – 2014, het veertiende evaluatierapport, LETB XIV 2019.

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van Ravesteyn NT, Broeders MJM, **Kregting LM**, Otten JDM, Heijnsdijk EAM, verbeek ALM, de Bruijn AE, de Koning HJ, Pijnappel RM, Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker (LETB). Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland, het vijftiende evaluatierapport, LETB XV 2023.

PORTFOLIO

Courses	ECTS	Hours	Year
EWP02 Advanced topics in decision-making in medicine	2.4		2019
CE16 Using R for decision modelling in health technology assessment	1.1		2019
HS05 Planning and evaluation of screening	1.4		2019
EP13 Cancer epidemiology	1.4		2019
CE15 Advanced decision modelling	1.4		2019
Scientific integrity for PhD students	0.3		2019
Workshop growth modelling		8	2019
Snel lezen, geheugentechnieken en mindmappen	0.6		2020
Biomedical writing course	2.0		2020
Python beginner course		10	2020
ESP70 Fundamentals of medical decision making	0.7		2020
ESP77 Advances in clinical epidemiology	0.7		2020
Extension BROK certificate		6	2021
Job orientation		12	2022
Total courses	*12.0*	*36*	
Conferences and seminars			
Lunch seminars MGZ		96	2018-2022
Club meth meetings	1		2018-2022
Journal club meetings		23	2018-2022
Attendance and poster presentation ICSN 2019 Rotterdam	1		2019
Attendance 'Evolutie of revolutie? Praat mee over de wetenschapper in 2030' Den Haag		8	2019
Attendance and poster presentation EBCC 2020 (online)	1		2020
Oral presentation EBCC 2020 (online)	1		2020
Attendance SMDM online meeting – Covid-19 modelling		4	2020
Vereniging van Epidemiologie: webinars and seminars		11	2020-2021
Oral presentation NABON plenary meeting		8	2020
Erasmus MC graduate school PhD day	0.2		2021
Attendance and poster presentation RIVM meeting 'Bevolkingsonderzoeken in beeld (en geluid)'		20	2021
Attendance and poster presentation WEON 2022	1		2022
Attendance pre-conference workshop WEON 2022 'lifelong learning'		2	2022
Attendance and poster presentation EBCC 13 Barcelona	*1*		2022
Attendance and poster presentation ICSN 2023 Turin	*1*		
Oral presentation ICSN 2023 Turin	*1*		
Total conferences and seminars	*8.2*	*172*	

Teaching			
Supervision of medical students – 'Community project' 3rd year curriculum Medicine, Erasmus MC		75	2019-2022
Evaluating Bachelor essays, 3rd year curriculum Medicine, Erasmus MC		40	2020
VO secundaire preventie, curriculum Clinical Technology, Erasmus MC/ TU Delft		6	2021
Assisting in teaching' HS05 Planning and Evaluation of Screening' at NIHES		16	2021-2022
Master consultancy for master theses by medical students		10	2021-2022
VO keuzen in de zorg, 2nd year curriculum Medicine and Clinical Technology, Erasmus MC/ TU Delft		18	2021-2022
Total teaching	-	*165*	
Other			
Review articles for BMC Women's Health		20	2020-2022
Review article for Cancer epidemiology		8	2023
Total other	-	*28*	
Total	**20.2**	**401**	

DANKWOORD

Na vijf jaar is het einde in zicht. Het proefschrift is klaar en de verdediging is aanstaande. Het was een lange weg, die ik gelukkig niet in mijn eentje heb hoeven afleggen. Dit proefschrift is een product waar velen, direct en indirect, aan hebben bijgedragen. Een aantal hiervan wil ik in het bijzonder bedanken.

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