Optimization of breast cancer screening: informed decisions on benefits and harms

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Contents

CHAPTER 1

GENERAL INTRODUCTION

Breast cancer incidence, mortality, and survival

Incidence

Breast cancer is a major threat to women's health, becoming the most frequently diagnosed cancer globally when it surpassed lung cancer in 2020, and accounting for 11.7% of the 19.3 million new cancer cases diagnosed worldwide.[1] Not only is it diagnosed more often in older women than in younger women[2,3] but also there are clear geographic and socioeconomic differences in incidence. In 2020, the age standardized incidence in Western Europe was 90.7 per 100,000 women, which is much higher than the 26.2 per 100,000 women reported in South Central Asia.[1] In high-income countries, the age standardized incidence of breast cancer increased from 91.6 per 100,000 women in 2000 to 113.2 per 100,000 women in 2020.[1,4] Multiple factors have contributed to this increasing incidence over recent decades, but the most prominent are aging[5], declining fertility and delayed childbearing,[3] increased body mass index,[2] and the wide implementation of population-based mammography breast cancer screening.[1]

Mortality

Unsurprisingly, breast cancer is also the leading cause of cancer specific death among women. In 2020, breast cancer had the highest age standardized mortality rate for female cancer globally, killing 15.0 per 100,000 women and accounting for 15.5% of all cancer deaths.[1] Breast cancer mortality also varies by geography and socioeconomic status (SES), with the high mortality more common in low- and middle-income countries than in high-income countries. The age standardized mortality rate of breast cancer in high-income countries was 9.8–15.6 per 100,000 women in 2020, contrasting with 14.0–27.5 per 100,000 women in low- and middle-income countries.[1] The high mortality of breast cancer in low- and middle-income countries reflects their relatively weaker health care infrastructures and lower access to cancer screening services and treatment facilities.[1] Contrasting with the trend for the incidence of breast cancer to grow worldwide, mortality rates have decreased slightly over time in high-income countries in North America and Northwestern Europe, a situation that is counterbalanced by continued increases in low-income countries.[3,6–8] The decreasing mortality over time in high-income countries reflects improvements in cancer treatment and prevention.[1,4]

Survival

Although survival from breast cancer has improved substantially over recent decades in both high- and low-income countries,[9] differences in survival rates persist. The age standardized 5-year survival rate of breast cancer diagnosed from 2010 through 2014 in high-income countries has reached 85%, a figure that contrasts sharply with the 66% survival observed in women diagnosed from 2008 to 2015 in sub-Saharan Africa.[9] Improved

survival from breast cancer has closely followed improvements in cancer treatment and early diagnosis through population-based breast cancer screening, such that today, the 5-year survival from stage I breast cancer approaches 100% in high-income countries.[3,10] Despite substantial improvements in survival rates in low- and middle-income countries,[1] most patients in these countries still receive their diagnoses at advanced stages, possibly due to the lack of population-based breast cancer screening.[11,12] Mammography screening in most high-income countries has successfully shifted the stage of screen-detected breast cancers toward more early stages.[3,13–16]

Mammography screening for breast cancer

Breast cancer is a disease caused by DNA mutations or damage and is associated with multiple risk factors, such as aging, family history, hormone exposure, and lifestyle.[17] Multiple primary prevention efforts have sought to reduce exposure to modifiable risk factors.[18] Nonetheless, designing effective primary prevention strategies remains challenging because the precise causes are unclear.[19] Therefore, secondary prevention by mammography screening has prevailed over other prevention activities, achieving widespread implementation in most high-income countries.[13]

Mammography screening seeks to detect breast cancer before it becomes symptomatic, thus obtaining more time for early treatment.[20] Since the first randomized controlled trial (RCT) in New York in the 1960s, many high-quality RCTs have evaluated breast cancer mammography screening in high-income countries.[21] Because these RCTs showed 12%–58% mortality reduction in screened women,[13,22–24] many high-income countries implemented population-based breast cancer mammography screening programs from the 1980s.[25] Such screening is normally implemented as an organized program,[13,26] with quality ensured by systematically sending invitations and reminders to eligible women, double reading of mammograms, recalling women with abnormalities detected in screening, giving timely feedback of test results, and monitoring the program regularly.[13,27]

Some high-income countries also offer opportunistic screening as a complementary strategy to the organized program, while some low- and middle-income countries offer it as the main strategy.[3,13,28,29] Flanders, where most of the data studies in this thesis were performed, offers both organized and opportunistic screening.[30] Unlike organized screening, opportunistic screening does not use quality control measures routinely.[13] As the name suggests, opportunistic screening is primarily initiated by the spontaneous needs of women rather than systematic invitation.

In parallel to debates about the operation of screening, many continue to discuss both the necessity and the potential harm of screening.[22,23,31] Mammography screening may have reduced breast cancer specific mortality, but it may also lead to false-positive results, radiation-induced cancers, and overdiagnosis.[13,31] Therefore, the potential harms of screening must be quantified accurately and weighed against the benefits. Although these debates are unlikely to be resolved any time soon, they do stimulate important reflection about reliance on a recruitment strategy that invites women based solely on age.[32–36] Research has started to explore screening modalities that are better tailored to the characteristics of the target women, such as magnetic resonance imaging (MRI) [32,33] and digital breast tomosynthesis[34,35] for women with dense breasts, ultrasonography for women in low-income countries[36], and more intensive screening for women at high risk due to *BRCA* gene mutations.[36]

Overdiagnosis in mammography breast cancer screening

A major concern of breast cancer screening is the potential of overdiagnosis, which is defined as a screen detected breast cancer, that would otherwise not have caused symptoms or death during the women's lifetime.[31] Overdiagnosis is arguably the most important harm of mammography screening because detecting overdiagnosed breast cancers does not generate any health gains and does increase the physical, mental, and/or economic burden for both women and society. Although this unwanted side effect can be minimized, it cannot be avoided completely due to the large heterogeneity of breast cancers and silent disease reservoir that comprises non-progressive, slow-growing, and regressive cancers.[37] Detecting cancers in this silent reservoir inevitably leads to overdiagnosis.[38]

The key issue about overdiagnosis at the present time is its exact magnitude. Published data on overdiagnosis rates show an enormous variation, with some studies reporting no overdiagnosis[39,40] and others reporting overdiagnosis rates up to 80%.[41–43] For policy makers who need to weigh the benefits and harms of breast cancer screening, this large variability in current data is not very informative. Moreover, women need accurate estimates of overdiagnosis in order to make an informed decision about whether or not to take part in screening.[22,44]

Participation in mammography breast cancer screening

Breast cancer screening can only reduce mortality when women participate. Because organized breast cancer screening programs in most countries rely on invitations to reach eligible women, defining the participation rate as the proportion of invited women who attend has become the key quality assurance indicator for most programs.[27] The participation rate has also become a key factor for the cost-effectiveness of breast cancer screening programs.[45] The European quality assurance guideline for breast cancer screening recommends a participation rate of at least 70% as acceptable and a participation rate of at least 75% as desirable for organized breast cancer screening programs.[27] Participation below these thresholds reduces the cost-effectiveness of screening, although it does not mean that a 100% participation rate is necessary because the increased costs are only associated with marginal life-years gained.[45–47] While many published studies have looked at the association between screening participation and breast cancer diagnosis,[16,48] there is a paucity of evidence about the relationship between the regularity of repeated screening and the stage of breast cancer diagnosis.

Most member states of the European Union have implemented an organized breast cancer screening program,[49] but only moderate or average participation levels of 60% have been achieved.[50,51] At the same time, geographical inequity persists both between and within countries, with socioeconomic inequity an important driver. The participation rate in Northwestern Europe reaches 70% or above, while in Eastern Europe it is below 50%.[50,51] Within countries, women of low SES are consistently found to be less likely to take part in breast cancer screening.[48,52,53] Published data show that organized screening alleviates the inequity in participation while opportunistic screening exacerbates that inequity.[51,54]

Despite the breast cancer screening program in Flanders being operational for more than two decades, the participation rate is still relatively low. Only 50% of eligible women are screened in the organized breast cancer screening program, with a further 14% captured by opportunistic screening.[55] The determinants of low participation have been studied to improve participation in organized breast cancer screening,[56,57] but little is known about the screening situation in Flanders where both organized and opportunistic screening programs coexist. In this thesis, I describe efforts to study this topic in more detail. During these efforts, we obtained publicly available aggregated data on the sociodemographic status (SDS) and SES of all women eligible for screening and data from individual women about participation in screening and the diagnosis of breast cancer. In addition, we validated a "Simulation Model on Radiation Risk and breast cancer Screening" (SiMRiSc) and applied it to quantify overdiagnosis in the organized breast cancer screening in Flanders.

Aims and outline of this thesis

The research in this study was designed to address the following aims:

1. To evaluate the relation between regularity of repeated screening and the diagnosis of advanced stage breast cancer.
2. To evaluate the determinants of non-participation and coverage of population-based breast cancer screening in Flanders.
3. To evaluate the overdiagnosis of population-based breast cancer screening.

The thesis comprises nine chapters with seven original studies that can be broadly categorized into three parts. **Chapter 1** starts by giving a general introduction of the individual studies, which are detailed in **Chapter 2** to **Chapter 8**. Finally, **Chapter 9** summarizes the key findings of the thesis and explores the implications of our findings for the implementation of opportunistic and organized breast cancer screening, together with the thesis conclusions.

Part 1: impact of participation regularity on population-based breast cancer screening.

Chapter 2 evaluates the effect of repeated participation in population-based mammography screening on the risk of advanced stage breast cancer at diagnosis. This study links the participation and breast cancer diagnosis of women invited for breast cancer screening in Flanders from 2001 to 2017 at an individual level.

Chapter 3 evaluates the effectiveness of organized mammography screening for different breast cancer subtypes. In this study, we linked participation in breast cancer screening and the characteristics of diagnosed breast cancers at an individual level. This took the heterogeneity of breast cancer into account and evaluated the risk of being diagnosed with advanced or interval breast cancer for different molecular subtypes.

Part 2: determinants of participation in population-based breast cancer screening.

Chapter 4 presents a systematic review and meta-analysis that summarizes the determinants of non-participation in population-based organized breast cancer screening programs. We performed an extensive meta-analysis of the determinants of non-participation in breast cancer screening, excluding data from studies of opportunistic screening or that used self-reported data.

Chapter 5 provides an evaluation of the determinants of coverage for organized and opportunistic breast cancer screening in Flanders. In this study, we linked publicly available data on SDS and SES at the municipality level to the coverage rates of both organized and opportunistic screening from 2008 to 2016.

Chapter 6 compares the determinants of the coverage rate for organized and opportunistic breast cancer screening among women in the highest and lowest 10% by coverage rate. We applied publicly available data for organized and opportunistic screening coverage rates with the SDS and SES at a neighborhood level in Flanders. By using the highest and lowest percentiles covered by screening, this study further explored the determinants of inequity in screening coverage.

Part 3: estimation of overdiagnosis in breast cancer screening.

Chapter 7 evaluates a novel sensitivity model as a function of tumor size and applies it to the SiMRiSc microsimulation model. This sensitivity model has the potential to simulate the effect of mammography screening on breast cancer diagnosis more accurately. Building on the foundation of this study, we estimated overdiagnosis of invasive breast cancer in organized breast cancer screening program.

Chapter 8 evaluates the overdiagnosis rate in the Flanders population-based breast cancer screening program using the SiMRiSc model. We focused on the impact of the screening follow-up time and starting age on the level of overdiagnosis.

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PART 1

Regularity of participation in population-based breast cancer screening

CHAPTER 2

IRREGULAR SCREENING PARTICIPATION INCREASES ADVANCED STAGE BREAST CANCER AT DIAGNOSIS: A POPULATION-BASED STUDY

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Abstract

Objective To evaluate the effect of irregular screening behaviour on the risk of advanced stage breast cancer at diagnosis in Flanders.

Methods All women aged 50-69 who were invited to the organized breast cancer screening and diagnosed with breast cancer before age 72 from 2001 to 2018 were included. All prevalent screen and interval cancers within 2 years of a prevalent screen were excluded. Screening behaviour was categorized based on the number of invitations and performed screenings. Four groups were defined: regular, irregular, only-once, and never attenders. Advanced stage cancer was defined as a stage III+ breast cancer. The association between screening regularity and breast cancer stage at diagnosis was evaluated in multivariable logistic regression models, taking age of diagnosis and socio-economic status into account.

Results In total 13.5% of the 38,005 breast cancer cases were diagnosed at the advanced stage. Compared to the regular attenders, the risk of advanced stage breast cancer for the irregular attenders, women who participated only-once, and never attenders was significantly higher with $OR_{adjusted}$:1.17 (95%CI:1.06-1.29) and $OR_{adjusted}$:2.18 (95%CI:1.94-2.45), and $OR_{adjusted}$:5.95 (95%CI:5.33-6.65), respectively.

Conclusions In our study, never attenders were nearly six times more likely to be diagnosed with advanced stage breast cancer than regular attenders, which was much higher than the estimates published thus far. An explanation for this is that the ever screened women is a heterogeneous group regarding the participation profiles which also includes irregular and only-once attenders. The benefit of regular screening should be informed to all women invited for screening.

Keywords Breast Neoplasms, Digital Mammography, Neoplasm Staging, Screening Participation, Regularity

Introduction

Female breast cancer is a commonly diagnosed cancer, representing one fourth of all newly diagnosed cancers in women worldwide.[1] The stage of breast cancer at diagnosis is a significant prognostic factor for the overall survival rate for breast cancer.[2] The five-year survival rate for stage I breast cancer has approached 100%, but declines to less than 30% for stage IV breast cancer.[2,3] A contributing factor for the observed decrease in breast cancer mortality is the shift to early stages of breast cancer at diagnosis.[4] At the population level, earlier stage diagnosis of breast cancer can be achieved by implementing a breast cancer screening programme, with sufficient quality and participation rates.[5,6] In many European countries, mammography screening is offered in a systematic way in population based programmes, but co-exists alongside opportunistic screening[7], in which mammograms are offered at women's request or during regular healthcare checkups.[6]

In randomized controlled trials (RCTs), the non-screened control groups have a higher risk of advanced stage breast cancer than the screened group.[8,9] The effect of screening on cancer stages at diagnosis at the population level has been evaluated in some ecological studies, in which a reduction of advanced stage breast cancer incidence has been observed in women who participated in screening compared with non-participants.[5,10] Some studies that used data at an individual level have also indicated that non-participation is associated with advanced breast cancer stages.[11–13] However, in these studies the breast cancer stages at diagnosis were only compared between the ever and never screened women.[11–13] Within the ever screened group, women could have participated in screening with variable intervals between consecutive rounds, impacting screening regularity. However, such detailed investigation of screening regularity requires the linkage of data of the invited women at individual level from multiple sources, which can be difficult to perform. In published studies thus far, no quantitative evidence is available about the effect size of regular screening on the risk of advanced stage breast cancer at diagnosis.

The aim of this study was, therefore, to evaluate the association between stage at time of diagnosis and breast cancer screening regularity, using individual level data from women eligible for breast cancer screening residing in Flanders, Belgium.

Method

Breast cancer screening in Flanders

Since 2001, the population-based organized breast cancer screening programme has been implemented by the Center for Cancer Detection (CCD) in the whole region of Flanders. All women aged 50-69 with no history of breast cancer are eligible to participate biennially. The cost of the organized screening is fully covered by the universal health insurance system in Flanders. The quality of the organized screening programme is ensured by systematic quality control measures, following European guidelines.[14] Besides the organized screening programme, opportunistic screening may be performed on the spontaneous initiative of the woman or her physician. The opportunistic screening practices existed even before the organized screening programmes and have remained an option for screening for a large proportion of women ever since. In 2016, the percentage of eligible women who were covered by the organized and opportunistic screening was 50.0% and 14.1%, respectively.[15] Of note, opportunistic screening is not subject to systematic quality control, and is only partially reimbursed by the health insurance system. The organized screening programme in Flanders invited all eligible women until the year 2017.

Since opportunistic screening covers a sizeable proportion of women who are eligible for screening, the Belgian Cancer Registry (BCR) includes both the organized and opportunistic screening in participation profiles. An opportunistic screening mammogram was defined as a mammogram performed outside the organized screening programme. However, mammograms that occurred within 3 months following a positive organized screening and/or within 3 months prior to cancer diagnosis were recognized as the diagnostic mammograms for the confirmation of breast cancer diagnosis rather than the opportunistic screening mammogram. All mammograms performed after a breast cancer diagnosis are not relevant to screening and were not taken into consideration.

Study design and data sources

The study cohort was constructed using individual level data from the CCD in Flanders, the BCR, and the InterMutualistic Agency (IMA). All data were routinely collected within the context of the organization and evaluation of the organized breast cancer screening programmes, as defined in the legal tasks of each data provider involved. [16] The CCD in Flanders provided the data on the participation in the organized screening programme from 2001 to 2017. The IMA collects all data of reimbursement health care from the universal health care system. [17] Whenever women participated in opportunistic mammography screening, the payment will be partially reimbursed by health insurance and the data will be transferred to the IMA database. For this study, the IMA provided information on mammograms outside the organized screening programme from 2001

to 2017. In addition, IMA data indicated persons who could benefit from increased reimbursement at the first invitation to screening of each woman, serving as a proxy for a weaker socio-economic position. Since an increased reimbursement is the social aid granted by the social security system for people who have experienced economic hardship, for women who have an increased reimbursement, a low socioeconomic status (SES) can be expected. The cancer diagnoses data were provided by the BCR and covered diagnoses in Flemish residents for the years 2001-2018. All women were informed that they could freely choose to refuse their data being used for research at the time of screening. The percentage of screened women who opt-out their data from research fluctuates around 1%. [15] All data were deterministically linked, using the national social security number as a unique personal identifier, according to existing data flows that are exerted in line with general data protection regulations (GDPR). Only pseudonymized data were used for this study, and results are reported in an aggregated way.

Definition of population, outcome and determinants

Population

The population for this study consisted of all women who were invited for organized breast cancer screening in Flanders and diagnosed with breast cancer from 2001 to 2018. Since only the information of breast cancer diagnosis between 2001 and 2018 was available, we only included women who had their last screening between 2001 and 2016 to ensure all women have a maximum 24 months of follow-up time after the last screening and identify breast cancers related to screening. Since women older than 69 were no longer invited to screening, we only included women who were diagnosed with breast cancer before age 72. Moreover, we excluded women who were only invited once, since the regularity of screening cannot be determined with a single screening invitation. All prevalent screen and interval cancers within 2 years of a prevalent screen were therefore excluded (Table S1).

Outcome

The outcome was the breast cancer stage at diagnosis, for breast cancers diagnosed prior to the age of 72. If multiple lesions were found in a woman, we only retained the most advanced lesion for the analyses (e.g. prioritising the invasive over the in situ lesion). A combined stage was considered in which pathological stage prevails over clinical stage, except for distant metastases, which were always considered stage IV. Stage was defined according to the applicable TNM edition. [18,19] Stages of breast cancer were determined at diagnosis before any treatment. A minor number of breast cancers were only recorded after neoadjuvant therapy and had reduced stage. As the stage at diagnosis for these breast cancers were not known, they were classified as stage unknown in the database by the BCR. We considered stages III and IV as advanced stages and stage I, II, and carcinoma in situ

as early stages. For breast cancers with unknown stages, the distribution of participation profiles of these cases was demonstrated in the descriptive analyses but not included in the regression models.

Determinants

The main determinant was the screening profile. A woman was considered *a regular attender* if she attended the organized and/or opportunistic screening at least twice, and the uptake was ≥70%, and the average interval of the attended mammography screening was between 20 and 28 months. The uptake of screening was used to ensure each woman had sufficient number of screenings, based on the similar idea of the 70% acceptable level of participation rate at the population level recommended by the EU guidelines, [14] and defined as the number of screenings attended, divided by the total number of screening opportunities. The total number of screening opportunities was determined by the length of time each woman was eligible for screening and the biennial screening interval. For women who were diagnosed with breast cancer before age 69, the endpoint of the eligible period was the time at breast cancer diagnosis. The average interval of the attended mammography screenings was defined as the length between the first and the last screening divided by the number of screenings. The average interval was defined as 20 to 28 months, rather than the fixed 24 months, in order to depict the flexibility of screening which could be rescheduled on women's demand. A woman was considered *an irregular attender* if she attended the organized and/or opportunistic screening at least twice, and the uptake was less than 70%, and/or the average interval was less than 20 months or over 28 months. A woman was considered as a *once in screening* when she participated only once in the screening after at least two invitations. All other women who never performed a screening after at least two invitations was categorized as *never attenders*. The multivariable logistic regression models were adjusted for age at diagnosis, and the SES, where an increased reimbursement status was used as an indicator for low SES.

Statistical analysis

The included women were stratified by their age at diagnosis, their screening participation profile, their breast cancer stage at diagnosis, and their increased reimbursement status. Data were reported as numbers and percentages. The association between the screening participation profiles and the risk of advanced stage breast cancer at diagnosis was first evaluated in a univariate logistic regression model, and consequently in a multivariable logistic model with adjustment for age at diagnosis and SES, which in literature has proven to be related to participation in screening and the stage of breast cancer at diagnosis [20,21]. The regularly screened women were used as the reference group in the regression model. The odds ratio (OR) and 95% confidence interval (CI) were reported for the risk of breast cancer diagnosed at the advanced stage.

Since the study population only included women with a diagnosis of breast cancer, overdiagnosis may lead to the diagnosis of more early stage breast cancers in the included breast cancers. Hence the relationship between participation regularity and the risk of advanced stage breast cancer at diagnosis can be biased. To evaluate the effect of overdiagnosis on the association between screening regularity and the risk of advanced stage breast cancer at diagnosis in our estimation, a sensitive analysis assumes a 10% overdiagnosis rate derived from the Dutch population [22,23] was performed, since the level of overdiagnosis in Flanders breast cancer screening programme has not been reported in literature, we applied the data from the Dutch population which is geographically nearby the Flanders region. [24–31] In this sensitivity analysis, a random 10% of early stage screen-detected breast cancers were excluded and the modeling was done in the rest of the cases, since by definition, overdiagnosis is due to the detection of breast cancer that are not progressive at early stage by screening mammograms. To evaluate the robustness of the effect of screening regularity on the risk of advanced stage breast cancer at diagnosis, an additional sensitivity analysis was performed in which advanced breast cancer defined as stage II or above. All statistical tests were two-sided with a significance level at 0.05. All analysis was performed in R 4.0.5.

Results

In total 38,005 women were diagnosed with breast cancer before age 72 from 2001 to 2018. The average follow-up years ranged between 6.4 years to 11.9 years for never attenders after at least two invitations and for women who were regularly screened, respectively. Of the diagnosed women, the total percentage of advanced breast cancer was 13.5%. Only 9.1% of breast cancers were diagnosed at advanced stage in the regularly screened women, which was lower than the 9.8% of the advanced stage breast cancer in the irregularly screened women. For women who only participated once in screening after at least two invitations, 16.3% of breast cancer were diagnosed at the advanced stage. Never attenders after at least two invitations had more than 30% of advanced stage breast cancer at diagnosis (Table 1). More advanced stage breast cancers were diagnosed in old women than the young ones (Table 1).

The multivariable logistic regression model showed that the risk of advanced stage breast cancer for the irregular attenders was higher than in the regular attenders, with OR: 1.17 (95%CI: 1.06-1.29) (Table 2). In the group who only participated once after at least two invitations, the risk of breast cancer diagnosed at an advanced stage was also higher than for regular attenders, with OR: 2.18 (95%CI: 1.94-2.45). Never attenders after at least two invitations had the highest risk of advanced stage breast cancer at diagnosis with OR: 5.95 (95%CI: 5.33-6.65) (Table 2).

Table 1 The number of women diagnosed with breast cancers and the percentage of breast cancers diagnosed at advanced stage in women of different participation profiles, incidence age groups, and increased reimbursement status.

Variable	BC cases	Advanced cases	
	Num	Num	%*
Total	38,005	5,149	13.5
Age group of women at breast cancer diagnosis			
50-54	4,221	457	10.8
55-59	9,957	1,295	13.0
60-64	10,595	1,492	14.1
65-71	13,232	1,905	14.4
Screening participation			
Regular	5,825	532	9.1
Irregular	22,019	2,156	9.8
Participated only once	6,018	982	16.3
Never attended	4,143	1,479	35.7
Increased reimbursement status**			
yes	4,571	726	15.9
no	33,434	4,423	13.2

**Row percentages were calculated for women in different groups.*
***An increased reimbursement status indicates women who are likely to have a low socioeconomic status.*

Table 2 Association between screening regularity and the risk of advanced stage breast cancer at diagnosis

Participation regularity	Model 1			Model 2		
	OR	95%CI	*P*	OR	95%CI	*P*
Regularly screened	ref	-	-	ref	-	-
Irregularly screened	1.10	(1.00-1.22)	0.060	1.17	(1.06-1.29)	<0.001
Participated only once*	2.00	(1.79-2.24)	<0.001	2.18	(1.94-2.45)	<0.001
Never attenders*	5.75	(5.15-6.42)	<0.001	5.95	(5.33-6.65)	<0.001

Model 1: univariate model
Model 2: multivariable model adjusted with age of women at breast cancer diagnosis, and socioeconomic status

In the sensitivity analyses, assuming a 10% overdiagnosis rate, the effect size of irregular screening and never attenders decreased slightly to OR: 1.15 (95%CI: 1.04-1.27) and OR: 5.63 (95%CI: 5.04-6.30), respectively (Table 3). The sensitivity analysis with the stage II+ breast cancer defined as advanced stage showed that the irregular attenders and never attenders remained statistically significantly more likely to be diagnosed with advanced

stage breast cancer than the regular attenders, and the effect size only had a minor change (Table 3).

Table 3 The effect of considering overdiagnosis and applying a different definition of advanced stage on the association between screening regularity and the risk of advanced stage breast cancer at diagnosis

Participation regularity	Model 1			Model 2		
	OR	95%CI	P	OR	95%CI	P
10% overdiagnosis rate						
Regularly screened	ref	-	-	ref	-	-
Irregularly screened	1.08	(0.98-1.20)	0.120	1.15	(1.04-1.27)	0.010
Participated only once*	1.95	(1.75-2.19)	<0.001	2.12	(1.89-2.38)	<0.001
Never attenders*	5.45	(4.88-6.08)	<0.001	5.63	(5.04-6.30)	<0.001
Stage II+ breast cancer as an advanced stage						
Regularly screened	ref	-	-	ref	-	-
Irregularly screened	1.12	(1.06-1.20)	<0.001	1.18	(1.11-1.26)	<0.001
Participated only once*	1.98	(1.83-2.13)	<0.001	2.11	(1.95-2.28)	<0.001
Never attenders*	5.92	(5.41-6.49)	<0.001	6.07	(5.54-6.65)	<0.001

Model 1: univariate model
Model 2: multivariable model adjusted with age of women at breast cancer diagnosis, and socioeconomic status
** For those who received at least two invitations.*

Discussion

Principal findings and comparison with published studies

In this study, we evaluated the effect of breast cancer screening regularity in women aged 50-69 years on the risk of breast cancer diagnosed at advanced stage. Irregular screening increased the risk of advanced stage breast cancer at diagnosis by 17% compared to regular screening. Women who participated only once in screening were twice more likely to be diagnosed with advanced stage breast cancer than the regular attenders. The never attenders had nearly six times higher risk of being diagnosed with advanced breast cancer than the regular attenders. Assuming a 10% overdiagnosis rate, the irregular attenders and never attenders remained statistically significantly related to higher risk of advanced stage breast cancer at diagnosis with the effect size slightly decreased.

In the literature, never attenders have a higher odds ratio of being diagnosed with advanced stage breast cancer than ever screened women, with the reported effect size ranging from

1.41 to 2.05.[21,32–35] In our analysis, the risk of advanced stage breast cancer at diagnosis was nearly six times higher for the never attenders than the regularly screened women. This may be because we compared the never attenders with the regularly screened women rather than just ever screened women. The finding suggests that previous studies underestimate the effect of regular screening, as they grouped women who only participated once in screening with the regularly and the irregularly screened women. Although overdiagnosis in screening may increase the percentage of early stage breast cancer at diagnosis hence affect the association between screening regularity and the risk of advanced stage breast cancer at diagnosis, we found that never attenders remained more than 5 times more likely to be diagnosed at advanced stage breast cancer than regularly screened women even when 10% overdiagnosis was adjusted in the sensitivity analyses.

Strengths and limitations

The strength of this study is that the participation data and the breast cancer stages were available at the individual level. We applied a strict definition of screening regularity with both the number of screenings and the interval between screenings considered. The regularity of screening was determined based on a longitudinal history of screening, adding granularity to the assessment of the effect on the risk of advanced stage breast cancer at diagnosis, as compared to previous reports purely discriminating ever from never screened women. Moreover, the inclusion of the participation data in the opportunistic screening contributed to a more comprehensive evaluation of the effect of screening.

The study also has some limitations. First, due to privacy regulations, the comparison was made within the women who were diagnosed with breast cancer, not within the population invited for breast cancer screening. Therefore, the effect size measured by odds ratios in our study cannot be interpreted as the probability of advanced breast cancer. Another limitation is that we did not have access to the tumor grade on an individual level. For that we were not able to just assess grade 2 and 3 invasive cancers in the estimated risk of overdiagnosis. However, the 10% overdiagnosis in the sensitivity analysis was considered a reasonable estimate.[6,23,36] Lastly, some cases have unknown stages in the database and cannot be used in the estimation of screening effect on cancer stages. We calculated the proportion of these cases and found they only account for 3.6% of the total cases. Furthermore, the distribution of participation profiles of all cases changed only slightly after the exclusion of cases with unknown stages, indicating the exclusion of unknown stages has only a minor impact on the participation profiles of the included cases.

Interpretation and policy implications of the findings

In order to achieve the effect of early detection and mortality reduction, the breast cancer screening programme requires more than 70% of eligible women to actually be screened.

[14] In our results, the never attenders had the highest risk of advanced stage breast cancer. This group could have benefited from breast cancer screening as regards the reduction of advanced stage cancer, had they participated in screening. Therefore, more intensive effort should be made to encourage the never attenders to participate in screening.

Among women who participate in screening, the irregular attenders have a 17% higher risk of having advanced stage breast cancer than the regular attenders. To achieve regular screening, women do not only have to participate in an adequate number of screenings but also need to participate within the recommended interval. This interval is set at 24 months in Flanders, as it is in many European countries.[7] The benefits and the importance of screening regularity should be highlighted in the breast cancer screening programme promotional materials. such as the invitation letters and the brochures.

Interestingly, compared with the regular attenders, women who only participated once in screening had an more than two times higher risk of advanced stage breast cancer at diagnosis. This clearly suggests that women who ever participated in screening are a heterogeneous group, and the broad categorization of women into the ever screened and never screened groups in literature may lead to under-estimation of the effect of regular screening. Women who only participated once in screening before they were diagnosed with breast cancer are highly likely to experience symptoms and attend the screening for confirmation. Since symptoms can occur at any age, these women should be encouraged to participate earlier, before they have symptoms, preferably at the age of 50 when they receive their first invitation for screening.

Conclusions

Never attenders were nearly six times more likely to be diagnosed with advanced stage breast cancer than regular attenders, which was much higher than the effect size that used ever screened women as the reference in literature, indicating that the effect of regular screening was under-estimated in the literature. Irregular screening increases the risk of advanced stage breast cancer by 17%. Women who participate only once in screening are twice as likely to be diagnosed with advanced stage breast cancer, indicating they may have symptoms. The benefit of regular screening, and the risk of not participating in screening until symptoms appear, should be made clear to all women who are eligible for screening.

Table S1 Excluded cases diagnosed after prevalent screen and after only one failed attendance

Group	Breast cancer cases	Advanced cases
Prevalent screens related	6,291	469 (7.5%)
After one failed attendance	301	103 (34.2%)

Additional Information

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Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement: The access to the data is possible with the approval from the InterMutualistic Agency, the Belgian Cancer Registry, and the Center for Cancer Detection in Flanders. Further information is available from the corresponding author upon request.

Ethics Statement: Consent from the participants was obtained at the time of screening. Only pseudonymized data were used for this study, and results are reported in an aggregated way. Ethics approval was waived for this study. The study was performed in accordance with the Declaration of Helsinki.

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CHAPTER 3

EFFECTIVENESS OF ORGANIZED MAMMOGRAPHY SCREENING FOR DIFFERENT BREAST CANCER SUBTYPES

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Abstract

Background Screening program effectiveness is generally evaluated for breast cancer (BC) as one disease and without considering regularity of participation, while this might have an impact on detection rate.

Objectives To evaluate the short-term effectiveness of a mammography screening program for the major molecular subtypes of invasive BC.

Methods Included were all women who participated in the screening program and were diagnosed with screen-detected or interval BC in Flanders (2008- 2018). Molecular subtypes considered were luminal and luminal-HER2-positive, human epidermal growth factor receptor 2-positive, and triple-negative BC (TNBC). The relationship between the BC stage at diagnosis (early (I-II) versus advanced (III-IV)) and the way of detection (screen-detected or interval) as well as the relation between the way of detection and participation regularity (regular versus irregular) was evaluated by multi-variable logistic regression models. All models were performed for each molecular subtype and adjusted for age.

Results Among the 12,318 included women, BC of luminal and luminal-HER2-positive subtype accounted for 70.9% and 11.3%, respectively. Screen-detected BC was more likely to be diagnosed at early stages than interval BC with varied effect sizes for luminal, luminal-HER2-positive, and TNBC with OR:2.82 (95%CI:2.45-3.25), OR:2.39 (95%CI:1.77-3.24), and OR:2.29 (95%CI:1.34-4.05), respectively. Regular participation was related to a higher likelihood of screening detection than irregular participation for luminal, luminal-HER2-positive, and TNBC with OR:1.21 (95%CI:1.09-1.34), OR:1.79 (95%CI:1.38-2.33), and OR:1.62 (95%CI:1.10-2.41), respectively.

Conclusions Regular screening as compared to irregular screening is effective for all breast cancers except for the HER2 subtype.

Key words Breast Neoplasms; Early Detection of Cancer; Immunohistochemistry; Biomarkers; Social Participation

Introduction

Invasive breast cancer is a common heterogeneous disease.[1] The main subtypes are luminal, luminal-HER2-positive, human epidermal growth factor receptor 2 (HER2) positive, and triple negative breast cancer (TNBC).[2,3] In 2020, breast cancer accounted for one in four newly diagnosed cancer cases and one in six cancer deaths worldwide in women.[4] Population-based organized mammography screening programs have been implemented widely in high income countries based on screening's proven long-term effect regarding mortality reduction. In randomized controlled trails (RCTs), screening has the potential to reduce up to 40% of breast cancer mortality for attenders.[5–7] However, the evaluation of the long-term effect of screening requires sufficient follow-up time because the effect of screening on breast cancer mortality takes at least 10 years to become evident.[8]

In parallel, many studies evaluated the short-term effect of screening regarding the stage of cancer at diagnosis and the mode of cancer detection (screen-detected or interval). In short term, a more favorable stage of screen-detected cancer compared to interval cancer indicates the effectiveness of screening because diagnosis at an early stage leads to a more favorable prognosis than at an advanced stage.[9] Strikingly, population-based studies on the evaluation of short-term effectiveness of screening normally considered invasive breast cancer as one disease.[10,11] It is well known that invasive breast cancers of different molecular subtypes can have different growth rates.[12,13] Population-based cohort studies showed that ER negative/HER2 positive breast cancers are considered as more aggressive and more likely to be diagnosed as an interval cancer.[13–16] It is not clear if all women diagnosed with different breast cancer molecular subtype benefit from screening equally. Therefore, to really evaluate the effectiveness of breast cancer screening, it is necessary to consider the major molecular subtypes of breast cancer.

The value of breast cancer screening programs is the detection of breast cancer in an early stage.[9] Compared to screen-detected breast cancers, interval cancers generally have more advanced stages and a poorer prognosis.[14] When evaluating the short-term effectiveness of a breast cancer screening program, the number of visits and regularity of participation need to be taken into account.[17] Indeed, regularity of screening attendance can affect both the mode of detection (screen-detected or interval) and the stage at breast cancer diagnosis.[14,16,18] Few studies have attempted to evaluate the effect of consecutive participation in screening and reported that women who participated in the last two screenings before diagnosis have a lower risk of breast cancer than women who participated in only one or none of the last two screenings before diagnosis.[19–21] However, these studies only considered the number of screening rounds women participated in, without considering the effect of the regularity of screening participation.

The aim of this study was to evaluate the short-term effectiveness of a population-based organized breast cancer screening program when the role of screening regularity and main molecular breast cancer subtypes are considered. To that goal, we linked the data of screening participation and diagnosed breast cancer molecular subtypes at the individual level. As molecular subtypes are not commonly investigated for in-situ breast cancers, we only included the invasive breast cancers for this study.

Methods

The inclusion and exclusion criteria of the study population

This study included all women who were ever screened in the population-based organized breast cancer screening program in Flanders and diagnosed as screen-related invasive BC (diagnosed ≤ 24 months after screening) from 2008 to 2018. Since the information of breast cancer stage and hormone receptors was only available from 2008 to 2018, we excluded women who had their last screening after 2016 to ensure all women had a complete follow-up time of 24 months after their last screening. In addition, all prevalent screen-detected and interval cancers within 2 years of a prevalent screen were excluded.

The biennial invitation to the organized breast cancer screening program for all women aged 50 to 69 with no history of breast cancer in Flanders was started in 2001.[22] The breast cancer screening program was implemented in an organized way in the sense that a dedicated center for cancer detection (CCD) was installed for the organization of the program with systematic quality control measures consistent with the European guidelines.[17,22] No extra exams besides the mammography screening test were provided at the time of screening. Furthermore, at the time of screening, no extra explanation was provided unless women specifically asked for it.

Data sources

The Belgian Cancer Registry received approval (reference number 14/115) from the Belgian Sectoral Committee of Social Security and Health to collect and deterministically link Belgian Cancer Registry (BCR), population-based mammography screening program and InterMutualistisch Agentschap (IMA) data, using the social security number as a unique patient identifier to evaluate the quality of breast cancer screening in Flanders. The individual level data on the participation in the screening program and the breast cancer diagnoses were linked from the CCD and the BCR respectively. Specifically, the CCD provided age, screening date and screening results of participating women, and the BCR provided the cancer incidence date and the age at time of diagnosis, and pathological characteristics including stage, and estrogen receptor (ER), progesterone receptor (PR)

and human epidermal growth factor receptor 2 (HER2) status. Stages were defined according to the TNM classification system, and pathological stages were prioritized over clinical stages with the exception of distant metastases which were always considered stage IV. Invasive breast cancers that were down staged following neoadjuvant therapy were classified with unknown stage. All data were linked at the individual level using the national social security number as a unique personal identifier. Only pseudonymized data were available to the researchers, within a strictly secured environment in line with the European Union General Data Protection Regulation. Moreover, the informed consent from the participants was obtained at the time of screening (Supplementary Materials). All women were informed with the option to opt out of the use of their data for any research purpose at the time of screening. The rate of activated opt-out in the past years was around 1% of the screened women.[22]

Outcomes

In this study, the short-term effectiveness of the screening program was primarily characterized by the percentage of early-stage breast cancers and secondary by the percentage of screen-detected breast cancers. Therefore, the primary outcome was the stage of invasive breast cancer at diagnosis categorized into early stage (I, II) and advanced stage (III, IV). The secondary outcome was the breast cancer detection mode: screen-detected breast cancers were defined as diagnosed within 3 months of the first diagnostic assessment that followed a positive screen (but at the latest within 24 months of screening), whereas interval breast cancers were defined as diagnosed within 24 months after a negative screening or diagnosed more than 3 months after the first diagnostic assessment that followed a positive screen (but at the latest within 24 months of screening).

The molecular subtypes were approximated by the joint expression of ER, PR and HER2 status [2]. All cancers were categorized into five groups: luminal with ER and/or PR positive and HER2 negative; luminal-HER2-positive with ER and/or PR positive and HER2 positive; HER2-positive with ER and PR negative and HER2 positive; the TNBC with ER, PR and HER2 negative; all other cancers were categorized into the group with unknown molecular type.

Determinants

Screening regularity: The regular screening participants were defined as women who had a per woman uptake of screening $\geq$ 70% and a per woman averaged screening interval $\geq$ 20 months and $\leq$ 28 months. Based on a similar idea of the participation rate for the whole population[17], the per women uptake of screening was defined as the number of screenings attended divided by the total number of screening opportunities. For women who were diagnosed before age 69, the end point of the calculation of screening opportunity was

the cancer diagnosis date. Therefore, the irregular screening participants were defined as women who had a per women uptake of screening < 70% and/or had an average screening interval > 28 months or < 20 months. We applied the 20 to 28 months rather than a fixed 24 month average screening interval in the definition of screening regularity in order to account for the variability in the screening interval in practice. Age at diagnosis: the age of women at the diagnosis of invasive breast cancer was categorized into four age groups, 50-54, 55-59, 60-64, and 65-71.

Statistical analysis

For the primary outcome, the likelihood of early-stage diagnosis was compared between screen-detected and interval cancers first with univariate logistic regression models and subsequently with multivariable logistic regression models with adjustment of age at diagnosis and screening participation regularity. Invasive breast cancers with unknown stage were not included for this analysis. For the secondary outcome, the likelihood of diagnosis as screen-detected was compared for regular and irregular screening with multivariable logistic regression models with adjustment of the age at diagnosis. All analyses were performed for breast cancers of different molecular subtypes separately.

For the primary outcome, we performed a sensitivity analysis to account the potential impact of overdiagnosis on the stage of cancer diagnosis. Since overdiagnosis of cancer can be defined as the detection of cancer that would have never become symptomatic if not screened.[23] Thus, overdiagnosis can dilute the proportion of advanced stage cancers. In the sensitivity analyses, a 10% of screen-detected early-stage breast cancer was assumed as overdiagnosed and randomly excluded. As the overdiagnosis rate in the Flanders breast cancer screening program is not reported in literature, we applied this published data from the Dutch population.[23,24]

Odds ratio (OR) and corresponding 95% confidence interval (CI) were reported as the effect size from the regression models. All statistic tests were two-sided with a statistic significance level at 0.05. The analyses were performed in R 4.0.5.

Results

In total 12,318 women were diagnosed as screen-related breast cancer and included in this study, of which luminal was the most commonly diagnosed breast cancer and ac-counted for 70.9% of the total diagnosed breast cancers followed by luminal-HER2-positive, TNBC and HER2-positive breast cancers at 11.3%, 4.7 %, and 1.8%, respectively (Table 1). The percentage of screen-detected luminal and luminal-HER2-positivebreast cancer

was 62.9% and 56.1%, respectively, while only less than 50% of TNBC and HER2-positive breast cancer were diagnosed by screening (Table 1). Overall, 87.3% breast cancers were diagnosed at early stage (I, II), only 1.6% (n=203) of all included breast cancers were classified as unknown stage. More breast cancers were diagnosed at early stage (I, II) in regularly screened women than irregularly screened women for overall, and the luminal and luminal-HER2-positive, and the triple negative breast cancers (Table 1).

Table 1 The number, % screen detected, % early stage of diagnosed breast cancers, in total and per molecular subtype, overall, and stratified by regular screenings behaviour and age category (N=12,318)

	Overall	Regular screening behavior		Age category at breast cancer diagnosis			
		Yes	No	50-54	55-59	60-64	65-71
All subtypes combined							
Total N	12,318	3,757	8,561	1,464	3,272	3,410	4,172
Screen detected %	61.0%	65.7%	58.9%	56.7%	59.6%	62.2%	64.2%
Early stage (I, II) %*	87.3%	88.8%	86.7%	87.1%	87.2%	87.3%	87.5%
Luminal							
Subtotal N (%)	8,739 (70.9%)	2,741	5,998	1,033	2,274	2,450	2,982
Screen detected %	62.9%	66.6%	61.2%	59.2%	61.2%	64.5%	64.2%
Early stage (I, II) %	88.7%	89.8%	88.3%	89.4%	88.9%	88.0%	89.0%
Luminal-HER2-positive							
Subtotal N (%)	1,386 (11.3%)	417	969	165	420	372	429
Screen detected %	56.1%	66.7%	51.5%	50.3%	53.1%	56.5%	60.8%
Early stage (I, II) %	81.8%	87.5%	79.4%	75.8%	80.5%	85.5%	82.3%
HER2 positive							
Subtotal N (%)	216 (1.8%)	65	150	29	52	54	81
Screen detected %	42.6%	36.9%	45.3%	51.7%	57.7%	35.2%	34.6%
Early stage (I, II) %	80.6%	76.9%	82.7%	75.9%	90.4%	87.0%	71.6%
TNBC							
Subtotal N (%)	573 (4.7%)	175	398	81	146	153	193
Screen detected %	44.3%	53.1%	40.5%	37.0%	44.5%	48.4%	44.0%
Early stage (I, II) %	86.4%	87.4%	85.9%	81.5%	85.6%	89.5%	86.5%
Unknown molecular type							
Subtotal N (%)	1,342 (11.4%)	345	997	148	361	363	470
Screen detected %	64.1%	69.6%	62.2%	60.1%	63.7%	64.2%	65.5%
Early stage (I, II) %	89.3%	87.8%	88.6%	91.9%	87.3%	87.6%	88.7%

** percentages of early stage calculated on the total amount with the 203 unknown stage cases included.*

Overall, the percentage of screen-detected and interval early-stage breast cancer was 93.0% and 82.2%, respectively. More screen-detected breast cancers were diagnosed at early stages than interval breast cancer for all molecular subtypes. In univariate logistic regression models the tests were statistically significant overall and for all molecular

subtypes except for the HER2 positive breast cancer (Table 2). In the multivariable logistic regression model, screen-detected breast cancer was statistically significantly related to a higher likelihood of early stage at diagnosis than interval breast cancer with OR: 2.84 (95%CI: 2.53-3.20). This was also the case for the luminal, luminal-HER2-positive, TNBC and unknown molecular subtypes with OR: 2.82 (95%CI: 2.45-3.25), OR: 2.39 (95%CI: 1.77-3.24), OR: 2.29 (95%CI: 1.34-4.05) and OR: 3.95 (95%CI: 2.75-5.73), respectively (Table 3). Regular screening was statistically significantly related to higher likelihood of screen-detection cancers overall with OR: 1.28 (95%CI: 1.18-1.40) and for breast cancer of luminal, luminal-HER2-positive, TNBC, and unknown molecular subtype with OR: 1.21 (95%CI: 1.09-1.34), OR: 1.79 (95%CI: 1.38-2.33), OR: 1.62 (95%CI: 1.10-2.41), and OR: 1.37 (95%CI: 1.05-1.81), respectively (Table 4).

The sensitivity analysis with 10% overdiagnosis rate showed that screen-detected breast cancer was statistically significantly related to a higher likelihood of early-stage breast cancer than interval breast cancer. The effect size, , decreased slightly compared to the results in table 3 for luminal (OR: 2.54 (95%CI: 2.20-2.93)), luminal-HER2-positive (OR: 2.15 (95%CI: 1.59-2.92)), TNBC (OR: 2.07 (95%CI: 1.21-3.67)), and unknown molecular subtype (OR: 3.56 (95%CI: 2.48-5.16)) (supplementary Table S1).

Table 2 Univariate logistic regression model for the comparison of the likelihood of early-stage breast cancer at diagnosis between screen-detected and interval breast cancer. (N= 12,115) *

	Early stage	Advanced stage	OR (95%CI)
Total			
Interval	3,864 (82.2%)	836 (17.8%)	ref
Screen-detected	6,893 (93.0%)	522 (7.0%)	**2.86 (2.54-3.21)**
Luminal			
Interval	2,664 (83.4%)	532 (16.6%)	ref
Screen-detected	5,091 (93.4%)	360 (6.6%)	**2.82 (2.45-3.26)**
Luminal-HER2-positive			
Interval	454 (76.9%)	136 (23.1%)	ref
Screen-detected	680 (89.2%)	82 (10.8%)	**2.48 (1.85-3.36)**
HER2 positive			
Interval	95 (79.8%)	24 (20.2%)	ref
Screen-detected	79 (88.8%)	10 (11.2%)	2.00 (0.92-4.60)
TNBC			
Interval	262 (83.7%)	51 (16.3%)	ref
Screen-detected	233 (92.1%)	20 (7.9%)	**2.27 (1.33-4.00)**
Unknown molecular type			
Interval	389 (80.7%)	93 (19.3%)	ref
Screen-detected	810 (94.2%)	50 (5.8%)	**3.87 (2.70-5.61)**

** The 203 breast cancers with unknown stage were not included, which accounted for 1.6% of the total included breast cancers.*

Table 3 Multivariable model for the comparison of the likelihood of early stage breast cancer at diagnosis for screen-detected and interval breast cancers (N= 12,115) *

Variable	OR (95%CI)					
	All	Luminal	Luminal-HER2-positive	HER2 positive	TNBC	Unknown molecular type
Mode of detection						
Interval	ref	ref	ref	ref	ref	ref
Screen-detected	2.84 (2.53-3.20)	2.82 (2.45-3.25)	2.39 (1.77-3.24)	1.79 (0.80-4.24)	2.29 (1.34-4.05)	3.95 (2.75-5.73)
Age at breast cancer diagnosis						
50-54	ref	ref	ref	ref	ref	ref
55-59	0.95 (0.78-1.16)	0.92 (0.71-1.18)	1.19 (0.73-1.90)	2.78 (0.67-12.38)	1.21 (0.55-2.59)	0.56 (0.26-1.13)
60-64	0.89 (0.72-1.09)	0.78 (0.61-1.00)	1.38 (0.83-2.29)	2.78 (0.67-11.70)	1.75 (0.75-4.06)	0.50 (0.23-1.00)
65-71	0.92 (0.75-1.12)	0.88 (0.68-1.13)	1.05 (0.63-1.72)	0.93 (0.25-3.10)	1.63 (0.71-3.67)	0.57 (0.26-1.14)
Screening regularity						
irregular	ref	ref	ref	ref	ref	ref
regular	1.15 (1.00-1.32)	1.20 (1.01-1.42)	1.48 (1.02-2.17)	0.67 (0.28-1.62)	0.75 (0.41-1.40)	0.92 (0.61-1.40)

** The 203 breast cancers with unknown stage were not included, which accounted for 1.6% of the total included breast cancers.*

Table 4 The effect of screening regularity on the model of breast cancer detection (screen-detected vs. interval) (N= 12,115)

Molecular type	Regular attenders vs. irregular attenders OR (95%CI)	
	Crude	Age-adjusted
Luminal	**1.26 (1.14-1.38)**	**1.21 (1.09-1.34)**
Luminal-HER2-positive	**1.85 (1.46-2.36)**	**1.79 (1.38-2.33)**
HER2 positive	0.64 (0.35-1.16)	0.95 (0.48-1.89)
TNBC	**1.64 (1.14-2.35)**	**1.62 (1.10-2.41)**
Unknown molecular type	**1.39 (1.07-1.81)**	**1.37 (1.05-1.81)**
Total	**1.32 (1.22-1.43)**	**1.28 (1.18-1.40)**

Table S1 Multivariable model for the comparison of the likelihood of early-stage breast cancer at diagnosis for screen-detected and interval breast cancer in sensitivity analyses with 10% assumption of overdiagnosis rate

Variable	OR (95%CI)					
	All	Luminal	Luminal-HER2-positive	HER2 positive	TNBC	Unknown molecular type
Mode of detection						
Interval	ref	ref	ref	ref	ref	ref
Screen-detected	**2.56 (2.28-2.88)**	**2.54 (2.20-2.93)**	**2.15 (1.59-2.92)**	1.60 (0.71-3.83)	**2.07 (1.21-3.67)**	**3.56 (2.48-5.16)**
Age at breast cancer diagnosis						
50-54	ref	ref	ref	ref	ref	ref
55-59	0.95 (0.78-1.16)	0.92 (0.72-1.18)	1.16 (0.71-1.85)	2.68 (0.64-11.90)	1.20 (0.54-2.58)	0.56 (0.26-1.13)
60-64	0.89 (0.73-1.09)	0.78 (0.61-1.00)	1.39 (0.83-2.30)	2.57 (0.62-10.85)	1.70 (0.73-3.96)	0.50 (0.23-1.01)
65-71	0.91 (0.74-1.11)	0.88 (0.69-1.13)	1.03 (0.62-1.69)	0.86 (0.23-2.86)	1.58 (0.69-3.56)	0.57 (0.26-1.13)
Screening regularity						
irregular	ref	ref	ref	ref	ref	ref
regular	1.15 (1.00-1.32)	1.20 (1.01-1.42)	1.47 (1.02-2.16)	0.70 (0.29-1.68)	0.76 (0.41-1.41)	0.90 (0.60-1.38)

Discussion

Main findings

In this study, we evaluated the shot-term effectiveness of the organized breast cancer screening program with the role of screening regularity and the major molecular subtypes considered. We found that for the most commonly diagnosed luminal breast cancers, more than 60% of the cancers were detected in screening and nearly 90% of the cancers were diagnosed at early stage, while less than 50% of TNBC and HER2-positive breast cancers were diagnosed by screening. Screen-detected breast cancer was statistically significantly related to higher likelihood of early stages at diagnosis than interval breast cancer for all the molecular subtypes except for the HER2 positive breast cancer. Regularly screened women were more likely to be diagnosed by screening than irregularly screened women.

Comparison with literature

Over 70% of breast cancers were diagnosed as luminal and more than 11% of breast cancers were diagnosed as luminal-HER2-positive in our study. Despite a large variation of the reported distribution of molecular subtypes in population-based cohort studies, the luminal breast cancer is the dominant type in all studies ranging between 54.8% and 77.6%.[1,15,16,25–29] The percentage of the luminal-HER2-positive breast cancer in our study is also comparable with the published studies ranged between 7% and 12.5%[1,15,16,25–29] In contrast the HER2 positive breast cancer and the TNBC which account for 1.8% and 4.7%, respectively in our study are less than published data in which the range of the HER2 positive breast cancer is between 3.0% and 9.7% and the range of the TNBC is between 7.9% and 12.0%.[1,15,16,25–30]

As is shown in published data, the low incidence of TNBC is age-related, around 37% of the cases of TNBC are diagnosed in women under the age of 50.[31] Thus, a possible reason for the lower level of the TNBC and HER2 positive breast cancer in our study compared to the published studies is that the published studies include women diagnosed in younger ages before 50, while we focused on a population with the age at breast cancer diagnosis $\geq$ 50. In addition, the hormone positive breast cancers (luminal and luminal-HER2-positive) have a later onset peak and the hormone negative breast cancers (HER2 positive and TNBC) have an earlier onset peak.[29] The studied population in our cohort has an older age at diagnosis and is therefore more likely to include more luminal and luminal-HER2-positive breast cancers and less TNBC and HER2 positive breast cancers. The low number of the TNBC and HER2 positive breast cancer in our study might also be related to a lower diagnostic rate of regular screening. These high proliferative breast cancers are more likely to be missed in regular screening. Since we performed the analyses for breast cancer of different molecular subtypes separately, the selection will not affect the evaluation of the effectiveness of screening.

We found that the luminal and luminal-HER2-positive breast cancers are more likely to be detected in screening than the TNBC and the HER2 positive breast cancers which is similar as reported in registry based cohort studies with women screened between 40 and 70 in Asian, European and North American countries.[13–15,32]

In our study, the screen-detected breast cancers had more favorable stage than interval cancers. Similar results are also reported in published studies and clearly indicate the short term effect of screening. Addition to these results, we further found that the screen-detected luminal and luminal-HER2-positive breast cancers were more likely to be early stage than the TNBC. For the HER2 positive breast cancers, screening is not effective. This observation is new and has never been reported in published studies which normally evaluated the effectiveness of screening for breast cancer as one disease. Furthermore, we also found that regularly screened women were statistically significantly more likely to be diagnosed in screening than irregularly screened women which is not previously reported.

Strengths and limitations

The strength of this study is that the included breast cancers were identified from a large population with more than a decade of follow-up time. The population-based screening participation data and breast cancer diagnosis data were linked at individual level.

The study also has limitations. First, the molecular subtypes of the diagnosed breast cancers were approximated by the combination of ER, PR and HER2 status. Breast cancer can be classified into more detailed groups with data like Ki67.[30,33] For example, there is an increasing number of studies showing that the TNBC is also a heterogeneous disease.[30] For this study, we did not have data for such further classification. Nevertheless, based on the current data, we did observe the different likelihood of early-stage breast cancer at diagnosis between screen-detected and interval breast cancer when the comparison was made for breast cancer of different molecular subtypes. Second, the molecular type of around 10% of the breast cancers in our study was unknown. Even so, the overall percentage of unknown molecular types is comparable with data reported in a study that used data from population-based cohorts in which breast cancers of unknown molecular types range between 7% and 20%.[27,28] Third, overdiagnosis is an inevitable unwanted results of screening, we do not know the exact level of overdiagnosis in our included population. We have tried to evaluate the impact of overdiagnosis on our results with a sensitivity analysis and found that screen-detected breast cancers remained statistically significantly related to early stage breast cancer at diagnosis in most breast cancer subtypes. Lastly, we did not obtained long-term follow-up data of the diagnosed breast cancers in different molecular subtypes. As is shown in published studies, although early stage breast cancer, no matter the subtype, has excellent 5-year distant relapse-free survival without chemotherapy[34],

prognosis of breast cancer of different molecular subtypes di-verged in long follow-up time.[35,36] For example, the ER- tumours appear to be less prone to death than ER+ tumours in a follow-up time longer than eight years after diagnosis[37] and the ER+ tumours have a significant high level of recurrence in long-term follow-up.[35] Future studies with long-term follow-up time are needed to evaluate the role of earlier diagnosis and the policy for adjuvant treatment and outcome.

Interpretation of the findings

Breast cancer is commonly reported in literature as one disease. However, it represents a spectrum of tumors with heterogeneous growth rates ranging from indolent to aggressive.[33] The most commonly diagnosed luminal and luminal-HER2-positive breast cancers are generally slow growing.[30,38] In contrast, the TNBC and the HER2 positive breast cancers are more aggressive and have shorter tumor volume doubling times [30,38] which lead to a shorter time window for screening to detect the tumors. In our results, we found the likelihood of early stage at diagnosis was significantly higher in screen-detected breast cancer than interval breast cancer. In addition, the odds ratio of early stage at diagnosis varied for breast cancer of different molecular subtypes and for HER2 positive breast cancer, the difference was not significant. This clearly verifies the heterogeneous nature of the diagnosed breast cancers and the necessity to evaluate the screening effectiveness with the major molecular subtypes of breast cancer considered.

In most of the high income countries, the selection of women eligible for screening is unanimously based on age of women and the biennial screening interval has been applied for decades. [5,39] The screening frequency has to be coherent with the tumor natural history in order to have most of the cancers diagnosed earlier in screening, especially for the more aggressive tumors.[14] Besides the suitable frequency of screening, an adequate number of screening exposures is also necessary. The European guideline for quality assurance in breast cancer screening and diagnosis recommends that 70% of women invited to screening need to be actually screened.[17] In our study, we took this quality indicator into account and further refined it by taking the interval between consecutive screenings into account and by defining the regularity of screening. We found that for breast cancer of luminal, luminal-HER2-positive, and TNBC subtypes, which accounted for 86.8% of the subtypes, regular screened women had a statistically significant higher likelihood of being detected by screening than the irregularly screened women. Our results suggest that organized breast cancer screening is effective for the majority of women eligible for screening and regular participation is key to achieving an effective screening.

For future studies, an interesting point for investigation is the characteristics of previous screening mammographies before breast cancer diagnosis. If radiology imaging markers

of the aggressive TNBC and HER 2 positive breast cancers can be identified on the mammograms, intervention could be developed and implemented in an early phase. Meanwhile, the cost-effectiveness of breast cancer screening is also an important point to consider for breast cancer of different molecular types. Especially for higher proliferative cases, cost-effectiveness of personalized screening should be evaluated before actual implementation.

Conclusions

Screen-detected breast cancer was related with higher likelihood of early stage breast cancer at diagnosis for all molecular subtypes except for HER2 positive breast cancer. Regular participation in organized breast cancer screening program was related to more screen-detected breast cancers for the luminal,luminal-HER2-positive, and TNBC subtypes which accounted for 86.8% of all diagnosed breast cancers. Women should be informed of the benefit of regular screening participation, encouraging them to participate regularly. Prediction models are needed to identify women of higher risk of proliferation to facilitate a more personalized screening scheme in the future.

Additional Information

Author Contributions: Conceptualization, L.D., M.J.W.G., G.V.H. and G.H.d.B.; methodology, L.D., M.J.W.G., G.V.H., B.V.d.V., and G.H.d.B.; software, L.D. and M.J.W.G.; validation, I.T., M.G., B.V.d.V., and H.D.S.; formal analysis, L.D. and I.T.; investigation, M.J.W.G., G.V.H. and G.H.d.B.; resources, G.V.H. and G.H.d.B.; data curation, I.T., M.G. and H.D.S.; writing—original draft preparation, L.D.; writing—review and editing, M.J.W.G., G.V.H. and G.H.d.B.; visualization, L.D., I.T.; supervision, G.V.H. and G.H.d.B.; project administration, M.G. and H.D.S.; funding acquisition, G.V.H. and G.H.d.B. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Access to the data is possible with the approval from the InterMutualistic Agency, the Belgian Cancer Registry, and the Center for Cancer Detection in Flanders. Further information is available from the corresponding author upon request.

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PART 2

Determinants of non-participation and coverage of population-based breast cancer screening

CHAPTER 4

DETERMINANTS OF NON-PARTICIPATION IN POPULATION-BASED BREAST CANCER SCREENING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background Breast cancer (BC) screening can be performed in a screening program (BCSP) or in opportunistic screening. The existing reviews on the determinants of non-participation depend on self-reported data which may be biased. Furthermore, no distinction was made between the probably different determinants of both screening strategies.

Objective To find the determinants of non-participation in BCSP by means of a meta-analysis.

Methods PubMed, Embase, and Web of Science were searched for observational studies which quantified factors associated with non-participation in BCSP in a general population. Studies on opportunistic screening, and studies using self-reported data were excluded. A random-effect model was used to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs). Potential sources of heterogeneity were explored by stratification of the results.

Results Twenty-nine studies with in total 20,361,756 women were included. Low income (OR: 1.20, 95%CI: 1.10-1.30), low education (OR: 1.18, 95%CI: 1.05-1.32), living far from an assigned screening unit (OR: 1.15, 95%CI: 1.07-1.24), being immigrant (OR: 2.64, 95%CI: 2.48-2.82), and having a male family doctor (OR: 1.43, 95%CI: 1.20-1.61) was associated with higher non-participation in screening. Reminders sent to non-attenders and estimations of ORs (adjusted or not) partly explained substantial heterogeneity.

Conclusion In this meta-analysis excluding studies on the non-participation in opportunistic screening, or with self-reported data on non-participation, the well-known determinants for non-participation are still significant, but less strong. This analysis supports the relevance of meta-analysis including only studies with registered non-participation in a BCSP.

Keywords: Breast cancer, mammography, mass screening, participation, determinant

Introduction

Breast cancer (BC) is the most frequent cause of female cancer death[1] and accounts for an estimated 11.6% of the total cancer deaths worldwide in 2018.[2] The risk of BC death can be reduced by 20% when BCs are detected at early stages by mammography screening.[3] A breast cancer screening program (BCSP) with mammography is therefore widely advised for early BC detection.[4] Compared with opportunistic BC screening that provides mammography screening on women's request and depends on women's healthcare insurance[5], a BCSP is population-based and characterized by actively inviting women to BC screening and comprehensive quality assurance activities such as training and audit of the program.[6]

Sufficiently high participation is a crucial element for the success of a BCSP. To ensure the performance and the public health impact of the population-based BC screening program, a 70% participation rate is recommended as an acceptable level of participation by the European guidelines for quality assurance in breast cancer screening and diagnosis.[6] While European countries had one of the earliest provided BCSP since 1986[7-8], the average level of screening participation in Europe was only 57.4% (range 27.4%-82.6%) in 2016.[9] Outside Europe, BCSP has an even lower participation rate ranging from 18.1% to 55.3% in 2016.[9-10]

There are several systematic reviews on determinants of non-participation in BC screening.[5,11-17] Main determinants for non-participation reported thus far are low income, low education, living in a rural area, being an immigrant, and comorbidity. However, these systematic reviews either combined results from BCSP and opportunistic screening settings, or included self-reported non-participation in BC screening. Studies showed that the self-reported non-participation tend to be over-reported by women.[18-19] Determinants of non-participation have not been reviewed and meta-analyzed specifically for registry data from BCSP. Therefore, we aimed to evaluate determinants of screening non-participation with registry based studies including recent publications with meta-analysis.

Methods

We conducted a systematic review according to the guideline of the Cochrane Collaboration[20] and reported the results following the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] The protocol of this systematic review was registered on PROSPERO (record number CRD42020154016).

Search strategy and study selection

Articles were identified in PubMed, Embase, and Web of Science. All databases were searched for studies published between January 1, 2010, and October 31, 2021. The search start year of 2010 was selected to balance the recency and efficiency as the screening guidelines and macro-social demographic factors changed over the last years. A detailed search strategy per database can be found in the Supplementary file. Additionally, the reference lists in the retrieved articles were searched to identify additional studies.

Inclusion and exclusion criteria

Observational studies were included if they examined the relationship between determinants and the non-participation of a BCSP with mammography and published in English. The non-participation in a BCSP was defined as the proportion of women who did not participate in the mammography screening within a required screening interval of a BCSP among all invited women. Studies were excluded in one of the following cases: the non-participation in an opportunistic BC screening was studied, the screening participation data were collected through self-reporting of participants, determinants of screening re-attendance were studied. Besides, case reports, letters, comments, editorials, reviews, and conference abstracts were excluded.

Two reviewers (LD, JW) independently conducted the screening of articles first based on title and abstract and then based on full text. Disagreements encountered were resolved through discussion or adjudicated by a third reviewer (GdB).

Data extraction and quality assessment

Two reviewers (LD, JW) independently extracted data regarding study characteristics (author, publication year, country, screening period and population size, determinants of non-participation, and non-participation rate), organizational characteristics of a BCSP (targeted age, screening interval, follow-up strategy and payment of screening), and odds ratio (OR) of the determinants of non-participation. In case the association represents determinants and screening participation, ORs were recalculated by 1/OR. The corresponding 95% confidence intervals (CIs) were recalculated likewise. If available, adjusted odds ratios (ORs) with 95% CIs were extracted. Otherwise, crude ORs and 95% CIs were extracted or calculated based on the number of screening non-attenders and attenders for each determinant.[22] If multiple articles were published with data of the same study population, determinants in the article that reported the OR with the most adjusted model or with the largest sample size was selected. However, if the articles that were published from the same study reported multiple unique ORs for different determinants of screening non-participation, they were all included for the different determinants in the meta-analysis. The quality of the included studies was assessed with the critical Appraisal

tool for Cross-Sectional Studies (AXIS).[23] The AXIS checklist intends to assess the validity and bias of cross-sectional studies with 20 questions in five domains including study aim, methods, results, discussion, ethical approval, and funding (see *Table S1*).

Statistical analysis

Determinants reported as categorical variables were dichotomized, in which the reference category applied in the study was tested against the other categories combined. OR and the corresponding 95% CI between the reference group and combined category was calculated.[22] Estimates of continuous variables were included or if needed, transformed from regression coefficients to ORs and 95% CIs. The inconsistency (I^2) test was used to measure heterogeneity. Under the assumption of heterogeneity, a meta-analysis using a random-effects model was performed for each determinant for which at least three studies were available. For each determinant, a stratified analysis was performed to explore the sources of heterogeneity. Based on the published studies, the factors that were related to the heterogeneity of non-participation were considered as stratified factors which included the type of invitation (any invitation or the first invitation), the interval of screening (24 months or 36 months), study region (North America, Europe or Asia), payment of screening (free or co-payment), reminders for non-attenders (yes or no) and estimations of ORs (adjusted or not). For the dichotomized determinants, the heterogeneity caused by the different categorization of determinants was also explored in the stratified analyses in which studies applied different categorizations were pooled separately. A sensitivity analysis was performed to evaluate the robustness of the pooled estimates by sequentially removing each study.[24] Publication bias was estimated using a funnel plot and assessed formally with Begg's test. All statistical analyses were performed with Stata 14 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the included studies

A total of 11,239 studies were identified in the search. A review of 5,299 titles and abstracts and 272 full texts resulted in 29 studies for the systematic review (Figure 1). Studies were from 11 countries where a BCSP was established (Canada, Denmark, Sweden, Norway, the United Kingdom (UK), France, Germany, the Netherlands, Israel, South Korea, and Australia). The total number of women in the included studies was 20,361,756, of which 14,944,899 were included in the meta-analysis. Three large studies from Asian countries (Korea, Israel, and Australia) took half of the total population size. The rest of the included women were of European or Canadian origin. The characteristics of the included studies are summarized in Table 1.[25-53] Twenty-two studies were included in the meta-analysis (Table S3).[26-28,31-41,44,46-47,49-53]

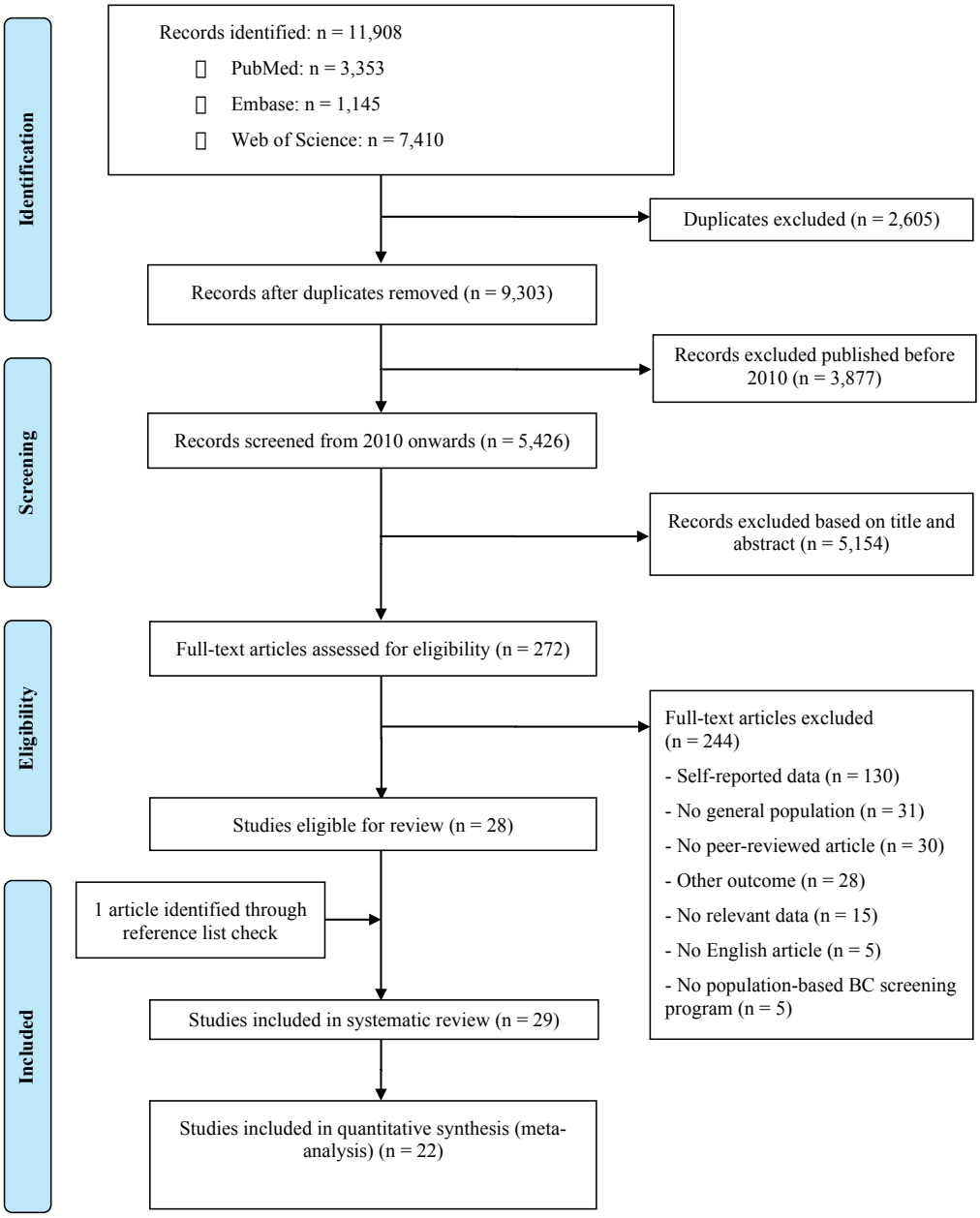

Figure 1 Flow chart of the study selection

Table 1 Characteristics of the included studies

Author, year	Country, screening year	Data source	Number of women	Target screening age, years	Screening interval, month	Fully subsidized	Reminder for all non-attenders	Non-participation %	Meta-analyzed determinants *
SS Hellmann, 2015[25]	Denmark, 1993-1999	Copenhagen mammographic screening register; Danish Diet, Cancer, and Health cohort baseline data	5,134	50-64	24	yes	yes	10.8	-
M Vahabi, 2015[26]	Canada, 2010-2012	Citizenship and Immigration Canada database; Ontario Cancer Registry; Ontario BC Screening Program database	1,407,060	50-69	24	yes	no	36.0	Income level, place of residence, family physician's gender
RH Jack, 2014[27]	UK, 2006-2009	London Quality Assurance Reference Centre database	159,078	50-52	36	yes	no	39.0	Income level
RR. Woods, 2018[28]	Canada, 2013-2014	Screening Mammography Program of British Columbia database; BC Cancer Registry database; Medical Services Plan physician payment file; Citizenship and Immigration Canada database	537,783	50-69	24	yes	yes	49.7	Age of women, income level, number of comorbidities
C Woodhead, 2016[29]	UK, 2010-2013	Clinical Record Interactive Search Lambeth DataNet	26,010	50-70	36	yes	no	44.2	-
CL Price, 2010[30]	UK, 2000-2002	Warwickshire, Solihull and Coventry Breast Screening Service database	18,730	50-70	36	yes	no	20.7	-
E Guillaume, 2017[31]	France, 2003-2012	French cancer screening management database	64,102	50-74	24	yes	yes	49.9	Age of women, income level, distance to an assigned screening unit

Table 1 continued

Author, year	Country, screening year	Data source	Number of women	Target screening age, years	Screening interval, month	Fully subsidized	Reminder for all non-attenders	Non-participation %	Meta-analyzed determinants *
SN Vigod, 2011[32]	Canada, 2002-2004	Ontario Breast Screening Program; Ontario Health Insurance Plan; Ontario Cancer Registry; Canadian Community Health Survey database	1,403	50-68	24	yes	no	39.2	Education level, number of comorbidities, marital status
C Renshaw, 2010[33]	UK, 2004-2007	London Quality Assurance Reference Centre database	742,786	50-70	36	yes	no	37.9	Age of women, income level
S Ouédraogo, 2014[34]	France, 2010-2011	French cancer screening management database	13,565	50-74	24	yes	yes	47.5	Age of women, income level, place of residence
S St-Jacques, 2013[35]	Canada, 2006-2008	Information system of the Quebec BC Screening Program; comprehensive Quebec Health Insurance Plan database	833,856	50-69	24	yes	yes	47.9	Age of women, income level, place of residence, distance to an assigned screening unit
LF Jensen, 2012[36]	Denmark, 2008-2009	Central Denmark regional cancer screening administrative database; Danish Cancer Registry; Statistics Denmark	144,264	50-69	24	yes	no	21.1	Income level, distance to an assigned screening unit, immigration status
M Le, 2019[37]	Norway, 1996-2015	Cancer Registry of Norway's databases; Statistics Norway	885,979	50-69	24	no	yes	26.0	Age of women, income level, education level, marital status, immigration status,
MN Zidar, 2015[38]	Sweden, 2011-2012	Radiological Information System; Statistics Sweden; Public Health Agency of Sweden; National Board of Health and Welfare; Swedish Social Insurance Agency	52,541	50-74	24	no	no	19.0	Age of women, distance to an assigned screening unit

Table 1 continued

Author, year	Country, screening year	Data source	Number of women	Target screening age, years	Screening interval, month	Fully subsidized	Reminder for all non-at-tenders	Non-par-ticipation %	Meta-analyzed determinants *
LF Jensen, 2015[39]	Denmark, 2008-2009	Central Denmark regional cancer screening administrative database; Danish Cancer Registry; Statistics Denmark; Danish National Patient Registry; Danish Psychiatric Central Research Register	144,264	50-69	24	yes	no	21.1	Age of women, education level, number of comorbidities, marital status
JT McDonald, 2017[40]	Canada, 1996-2011	Medicare Decision Support System; BC screening service database; Provincial Cancer Registry; Vital Statistics database of the Province of New Brunswick, Canada	91,917	50-69	24	yes	yes	45.0	Income level, place of residence, distance to an assigned screening unit, education level, marital status
EM Berens, 2014[41]	Germany, 2010-2011	Routine data from screening units and population registries in Duisburg, Bielefeld, Paderborn, Hamburg, and Berlin, Germany	423,649	50-69	24	yes	no	50.8	Age of women
LF Jensen, 2015[42]	Denmark, 2008-2009	Central Denmark regional cancer screening administrative database; Danish Cancer Registry; Statistics Denmark; Danish National Patient Registry; Danish Psychiatric Central Research Register	4,512	50-69	24	yes	no	14.9	-
LF Jensen, 2015[43]	Denmark, 2008-2009	Central Denmark regional cancer screening administrative database; Danish Cancer Registry; Statistics Denmark; Health Survey database in the Central Denmark Region	4,512	50-69	24	yes	no	14.9	-

Table 1 continued

Author, year	Country, screening year	Data source	Number of women	Target screening age, years	Screening interval, month	Fully subsidized	Reminder for all non-at-tenders	Non-participation %	Meta-analyzed determinants *
C Pornet, 2010[44]	France, 2004-2006	Database of the Association Mathilde, in charge of organizing BCS in Calvados; health insurance organizations database	4,865	50-74	24	yes	yes	44.3	Age of women, income level,
SH Larsen, 2018[45]	Denmark, 2008-2009	Central Denmark regional cancer screening administrative database; Danish Cancer Registry; Statistics Denmark; National Patient Register; National Pathology Data Bank	91,787	50-64	24	yes	no	20.2	-
LF Jensen, 2012[46]	Denmark, 2008-2009	Department for Public Health Programs database, Central Denmark Region; Statistics Denmark; Danish National Board of Health	13,288	50-69	24	yes	no	19.0	Family physician's gender
R Wilf-Miron, 2011[47]	Israeli, 2006-2008	Maccabi Healthcare Services (MHS) computerized billing system; MHS computerized Performance Measurement System; Israeli Census for data on socio-economic status ranks and ethnicity	157,928	50-74	24	yes	yes	31.2	Age of women, income level
D Roder, 2012[48]	Australia, 2001-2005	Australian BreastScreen program database; Australian Institute of Health and Welfare database	5,366,983	50-69	24	yes	no	44.9	-

Table 1 continued

Author, year	Country, screening year	Data source	Number of women	Target screening age, years	Screening interval, month	Fully subsidized	Reminder for all non-attenders	Non-participation %	Meta-analyzed determinants *
SM Tavasoli, 2018[49]	Canada, 2013-2015	Integrated Client Management System database for cancer screening program; Ontario Health Insurance Plan's Claims History databases; Ontario Cancer Registry and Pathology Information Management System; Client Agency Program Enrolment database and Corporate Providers Database; Canadian Institute of Health Information Discharge Abstract Database and National Ambulatory Care Reporting System	1,173,456	52-69	24	yes	no	47.6	Age of women, income level, place of residence, family number of comorbidities, physician's gender
B Vermeer, 2010[50]	the Netherlands, 2007–2008	Database of regional screening organizations	1,279,982	50-75	24	yes	yes	18.0	Immigration status
D O'Reilly, 2012[51]	UK, 2001-2004	Northern Ireland Quality Assurance Reference Centre; database of the Northern Ireland Longitudinal Study	37,059	48-64	36	yes	no	24.9	Age of women, place of residence, education level, number of comorbidities, marital status
DW Shin, 2020[52]	Korea, 2014-2015	Korean National Health Information Database	6,283,623	≥ 40	24	no	no	40.9	Income level, place of residence
JH Viuff, 2020[53]	Denmark, 2007-2010	The Danish Quality Database for Mammography Screening; The Danish National Patient Registry	650,003	50-69	24	yes	no	20.2	Age of women, number of comorbidities

** A full list of all the determinants reported by each study is shown in Table S2*

The risk of bias of the included studies was presented in Table S2. Requirements that were not satisfied were found for: sample size justification was unclear or missing in 10.3% of the studies; no measures were undertaken to address non-responders in 6.8% of the studies; basic data were not adequately described in 20.7% of the studies; limitations of the study were not discussed in 20.7% of the studies; sources of funding and conflicts of interest were not indicated in 6.8% of the studies, and ethical approval or consent of participants was not indicated in 17.2% of the studies.

Pooled estimates of the determinants of screening non-participation

Of all the 24 identified determinants (Table 1, Table S3), nine were included for the meta-analysis. The other determinants were reported by less than three studies or had inconsistent definition were not meta-analyzed. The characteristics of the studies that reported these determinants were described in table 1. All the determinates reported by the included studies were reported in table S3. Having low income (OR: 1.20, 95%CI: 1.10-1.30), being in younger age (OR: 1.09, 95%CI: 1.01-1.18), having low education (OR: 1.18, 95%CI: 1.05-1.32), living far from an assigned screening unit (OR: 1.15, 95%CI: 1.07-1.24), being unmarried (OR: 1.68, 95%CI: 1.32-2.14), being an immigrant (OR: 2.64, 95%CI: 2.48-2.82), and having a male family physician (OR: 1.43, 95%CI: 1.20-1.61) was associated with a higher non-participation in screening (Table 2, Figure S1-S5).

Stratified analysis and source of heterogeneity

Substantial heterogeneity was found among the studies that reported the above-noted nine determinants. The Index of Inconsistency (I^2) ranged from 90.6% to 99.8% for the studies which reported the education level and reported the age of women, respectively. (Table 2)

In the stratified analysis the heterogeneity decreased for the resident place when stratified by whether or not a reminder was sent to non-attendees. When there was no reminder for non-attendees, women living in an urban area showed a higher non-participation than those living in a rural area (OR: 1.14, 95%CI: 1.03-1.26). However, when a reminder was sent, women living in an urban area showed a lower non-participation than those living in a rural area (OR: 0.83, 95%CI: 0.82-0.84). (Table S4, Figure S6). For education level, distance to an assigned screening unit, and marital status, whether a reminder was sent to non-attendees or not partly explained the heterogeneity across the studies, where the heterogeneity decreased in the stratified analysis (Table S4).

For income level, number of comorbidities, and marital status reporting adjusted estimate or not in the included studies partly explained the heterogeneity across the studies, where in these stratified groups the heterogeneity decreased (Table S4). The heterogeneity of the dichotomized determinants: age of women, education level, and distance to an assigned

Table 2 Summary of determinants of screening non-participation in breast cancer screening programs

Determinants [a]	Number of studies	Number of women [b]	Non-participation %	Odds ratio	95% CI	I^2 %
Income level	14	12,500,262	32.7			99.6
high [c]		1,42,962	11.9-49.7	1.00	-	
low		4,804,875	12.0-51.1	1.20	1.10-1.30	
Age of women	14	5,721,776	31.5			99.8
old		1,060,746	8.0-53.3	1.00	-	
young [d]		4,545,696	12.6-52.0	1.09	1.01-1.18	
Place of residence	7	9,342,846	27.9			99.5
rural [e]		528,624	12.4-51.3	1.00	-	
urban		2,545,607	11.9-45.9	1.01	0.90-1.12	
Number of comorbidities	6	2,412,969	22.6			99.5
zero		2,101,610	12.0-51.7	1.00	-	
at least one		423,951	11.0-46.4	1.04	0.84-1.28	
Education level	5	1,160,622	24.6			90.6
high		73,651	19.8-29.0	1.00	-	
low [f]		951,464	21.1-25.1	1.18	1.05-1.32	
Distance to an assigned screening unit	5	1,186,680	43.6			94.5
small [g]		549,621	18.0-54.0	1.00	-	
large		538,237	20.1-47.6	1.15	1.07-1.24	
Marital status	5	1,160,622	23.5			99.4
married [h]		620,694	17.3-22.0	1.00	-	
unmarried		134,188	31.1-35.0	1.68	1.32-2.14	
Immigration status	3	2,310,177	20.5			95.9
non-immigrants		2,210,697	15.7-25.0	1.00	-	
immigrants [i]		99,480	34.3-49.0	2.64	2.48-2.82	
Family physician's gender	3	2,272,225	24.9			98.6
Female		949,434	12.7-29.0	1.00	-	
Male		1,322,791	11.4-37.0	1.43	1.20-1.61	

a: The first group of each determinant was the reference group.
b: For each determinant, the total number of women is larger than the sum of women in the stratified groups, because there are studies that only provided the effect size of a determinant without the cross-tables behind it.
c: The definition of high-income level varied in the included studies: "Most affluent 20%", "most affluent 30%" and "most affluent 50% and above" was applied in 8, 2, and 4 studies, respectively. The heterogeneity related to the different definition of high income was explored in the stratified analyses.
d:The definition of old age varied in the included studies: "60-64","60-69","67-69", "65-70" and "70-74" was applied in 1, 1, 1, 6 and 5 study, respectively. The heterogeneity related to the different definition of old age was explored in the stratified analyses.
e: The definition of urban area was based on the population size in which the rural area was defined as area with less than 2250 population in studies from UK. While the specific population size was not reported in studies from Canada and South Korea. The heterogeneity related to the different definition of rural area was explored in the stratified analyses.
f: The definition of low education level varied in the included studies: "< Secondary graduate", "<= 10 years education" and "< University graduate" were applied in 1, 2, and 2 studies, respectively. The heterogeneity related to the different definition of low education was explored in the stratified analyses.
g: The definition of small distance varied in included studies: "<= 2.5 km","<= 5 km","<= 10 km", and "<= 20 km", were applied in 1, 1, 1, and 2 studies, respectively. The heterogeneity related to the different definition of small distance was explored in the stratified analyses.
h: Married woman was defined as woman married or living with a partner.
i: Immigrant were defined as woman born abroad and both her two parents and four grandparents were born abroad.

screening unit were partly explained by the different categorization of determinants. For example, the heterogeneity of the education level decreased from 90.6% for the overall estimate to 78.6% in the stratified group that defined ≤ 10 years education as low education (Table 2, Table S4). (Table S4). However, the heterogeneity in almost all stratified groups with different categorization of determinants remained above a substantial level (I^2 > 50%).

Sensitivity analysis and publication bias

The pooled estimates of the determinants of screening participation were robust in the sensitivity analysis. The direction of the pooled estimates did not change when a single study was excluded sequentially (Figure S7). Publication bias was assessed for income and age of women. The Begg's test of the asymmetry of the funnel plot did not reach statistical significance P = 0.743 and 0.661, respectively (Figure S8-S9).

Discussion

Main results of this review

In this meta-analysis excluding studies with self-reported data on non-participation in screening and/ or studies on the non-participation in opportunistic screening, we found that lower income, younger age, lower education, living at a larger distance from an assigned screening unit, being unmarried, being an immigrant, and having a male family physician were associated with a higher non-participation in BCSPs. Women living in urban have higher non-participation in screening than women living in rural, however women living in urban have lower non-participation in screening when a reminder was sent to non-attenders. The heterogeneity of the pooled estimates were partially explained by whether or not a reminder was sent to non-attenders and whether or not the adjusted estimates were used.

Comparison with published studies

Compared with other meta-analyses that included non-participation data from opportunistic screening and/ or self-reported data, we found significant yet less strong association estimates with a narrower 95%CI for the well-known determinants of non-participation in screening. In our study, low-income women were more likely to not participate in a BCSP than high-income women (OR: 1.20, 95%CI: 1.10-1.30), whereas a meta-analysis reported a larger effect size with a wider 95%CI of low-income on non-participation in screening (OR: 1.35, 95%CI: 1.22-1.49).[12] Low educated women were more likely to not participate in a BCSP than high educated women. The effect size of low education on non-participation in screening was larger in a meta-analysis (OR: 1.61, 95%CI: 1.36-1.91) than our study (OR: 1.18, 95%CI: 1.05-1.32),[11] and the 95%CI was wider than our

study. Immigrants were more likely to not participate in a BCSP than non-immigrants. The effect size of immigrant status on non-participation in screening was smaller in a meta-analysis (OR: 1.85, 95%CI: 1.27-2.70) than our study (OR: 2.64, 95%CI: 2.48-2.82),[12] but the 95%CI was wider than our study.

The main possible reasons for the difference between our estimates and the published meta-analyses are two-fold. First, the registry and self-reported data were mixed and pooled together in these reviews published thus far. As women tend to over-report the utilization of BC screening, the estimates in these reviews can be influenced by recall bias.[18] Second, determinants of screening participation of a BCSP were not studied separately from an opportunistic screening in these reviews. However, a BCSP and an opportunistic screening have different implementation strategies,[4] and can cover different women groups in a population,[54] and have different determinants of non-participation in screening.[55] We, however, focused on population-based BC screening programs with registry data, which can avoid the recall bias. The smaller 95%CIs indicate that we provided more accurate estimates.

Interestingly, when a reminder was not applied, women living in an urban area were more likely to not participate in screening than women living in a rural area (OR: 1.14, 95%CI: 1.03-1.26). However, when a reminder was sent, women living in an urban area were related to lower non-participate in screening (OR: 0.83, 95%CI: 0.82-0.84) than women living in rural area. A meta-analysis has shown that a reminder is effective in motivating more women to participate in a screening program.[56] Our findings further suggest that the positive effect of a reminder plays a more important role in motivating women living in an urban area than women living in a rural area to attend a BCSP.

The pooled estimates for all the meta-analyzed determinants of non-participation in screening had substantial heterogeneity. Such heterogeneous estimates were also seen in other meta-analyses. For example, the I^2 of two reviews on the effect of living in a rural area and comorbidity on BC screening participation was 95% and 99%, respectively.[13,57] In our stratified analysis reminder sent to non-attendees or not and reporting adjusted estimate or not in the included studies partly explained the heterogeneity across the studies. Moreover, for the dichotomized determinants, since the contents/definitions of these determinants vary between the studies, pooled estimates are likely to be heterogeneous. In the stratified analyses, we found that the heterogeneity decreased slightly when studies were stratified based on the different categorization. As the results of the meta-analysis resembled to that of the original studies. It suggests that despite of wide variation in the categorization of determinants, their impact to non-participation was similar in each study. However, we were not able to fully explain the heterogeneity. Other potential explanations could be

the differences in study settings and methodologies of the included studies such as the different confounders that were adjusted for by different studies.

The study also has some limitations. First, only studies published in the English language were included; however, the publication bias was not statistically significant for the determinant income and age of women on screening non-participation. We would not expect a large difference between English or non-English publications for other determinants. Second, not all studies evaluated all nine determinants. Some determinants such as family physician's gender were only included in three studies. When a smaller number of studies are available, wider confidence intervals can be expected. Third, all the included studies were published from high-income countries where an organized breast cancer screening program was implemented. Moreover, half of the women included in the meta-analysis were of European or Canadian origin. Therefore, the results in this meta-analysis are less applicable to breast cancer screening globally. Lastly, the meta-analysis was based on data from the observational studies and most of the pooled ORs of the meta-analyzed determinants of non-participation in BC screening was below 2. Therefore, the determinants in our meta-analysis are less likely to be causally related to non-participation in BC screening.

Conclusions

In this meta-analysis excluding studies focusing on opportunistic screening, or using self-reported data, women who were characterized by low income, younger age, low education, living at a large distance to an assigned screening unit, being unmarried, being an immigrant, and having a male family physician were associated with a high non-participation in a BCSP. Interventions to improve the participation of BCSP need to pay more attention to women that are characterized by the above-noted determinants. The association between these determinants and non-participation in BCSP screening was significant but less strong than the report from the reviews including studies on the non-participation in opportunistic screening or with self-reported data on non-participation. This might be explained by a tendency of over-reporting screening utilization collected using a self-reporting method. This analysis supports the relevance of including only studies with registry data of the non-participation in BCSP.

Supplementary Material

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5

PRISMA Checklist continued

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5, 9 (Supplementary Material)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5 and Supplementary Material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5, 10-14 and Supplementary Material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5, 15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5 and Supplementary Material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6 and Supplementary Material
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Search strategy

PubMed:

("Breast Neoplasms" [Mesh] OR breast cancer* [tiab] OR breast tumo* [tiab] OR cancer of Breast [tiab] OR cancer of the Breast [tiab] OR breast carcinoma* [tiab] OR breast maligna* [tiab])

AND ("Mammography" [Mesh] OR mammogra* [tiab])

AND ("Mass screening" [Mesh] OR "Early Detection of Cancer" [Mesh] OR screening [tiab] OR early detection [tiab])

AND (attend* [tiab] OR complian* [tiab] OR uptak* [tiab] OR adher* [tiab] OR use [ti] OR usage [ti] OR participat* [tiab] OR non-participat* [tiab] OR rate [ti] OR rates [ti] OR screening behavio* [tiab] OR No-Show patients [Mesh] OR compliance [Mesh] OR facilities and services utilization [Mesh] OR social participation [Mesh] OR retention in care [Mesh] OR "Health Equity" [Mesh] OR "Healthcare Disparities" [Mesh] OR equity [tiab] OR inequity [tiab] OR equal* [tiab] OR inequal* [tiab])

AND ("Risk Factors" [Mesh] OR "Predictive Value of Tests" [Mesh] OR risk [tiab] OR predict* [tiab] OR deteminant* [tiab] OR factor* [tiab] OR relat* [ti] OR associat* [ti] OR "Population Characteristics" [Mesh] OR Socioeconomic factors [mesh])

Web of Science:

TS=((Breast cancer* OR Breast Tumor* OR Cancer of Breast OR Cancer of the Breast OR Breast Carcinoma* OR Breast Neoplasms OR breast maligna*) AND (Mammography OR mammogram*) AND (Screening OR Early detection OR Mass screening) AND (Attend* OR complian* OR adher* OR uptake OR facilities and services utilization OR Use OR usage OR participat* OR non-participat* OR social participation OR rate OR rates OR screening behavio* OR No-Show Patients OR retention in care OR Health Equity OR Healthcare Disparities OR equity OR inequity OR equal* OR inequal*) AND (Determinant* OR risk factor* OR predict* OR associat* OR relat* OR Population Characteristics OR Socioeconomic factor*))

Embase:

('Breast cancer*'/exp OR 'Breast Tumor*'/exp OR 'Cancer of Breast'/exp OR 'Cancer of the Breast'/exp OR 'Breast Carcinoma*'/exp OR 'Breast Neoplasms'/exp OR 'breast maligna*':ab,ti)

AND ('Mammography'/exp OR 'mammogram':ab,ti OR 'mammograms':ab,ti)

AND ('cancer screening'/exp OR 'mass screening'/exp OR 'mass radiography'/exp OR 'early cancer diagnosis'/exp)

AND ('patient attendance'/exp OR 'protocol compliance'/exp OR 'Adhere*':ab,ti OR 'health care utilization'/exp OR 'Usage':ab,ti OR 'refusal to participate'/exp OR 'Retention':ab,ti OR 'No-Show Patients':ab,ti OR 'uptake':ab,ti OR 'health equity'/exp OR 'health care disparity'/exp)

AND ('Determinant*'/exp OR 'risk factor*'/exp OR 'predictor*'/exp OR 'epidemiology'/exp OR 'population and population related phenomena'/exp)

Table S1: Items of the risk of bias assessment tool (AXIS)

Items	Content
Introduction	
1	Were the aims/objectives of the study clear?
Methods	
2	Was the study design appropriate for the stated aim (s)?
3	Was the sample size justified?
4	Was the target/reference population clear defined?
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?
7	Were measures are undertaken to address and categories non-responders?
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?
9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted, or published previously?
10	Is it clear what was used to determining statistical significance and/or precision estimates? (e.g. p-values, confidence interval)
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?
Results	
12	Were the basic data adequately described?
13	Does the response rate raise concerns about non-response bias?
14	If appropriate, was information about non-responders described?
15	Were the results internally consistent?
16	Were the results presented for all the analyses described in the methods?
Discussion	
17	Were the authors' discussion and conclusions justified by the results?
18	Where the limitations of the study discussed?
Other	
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?
20	Was the ethical approval or consent of participants attained?

Table S2 Quality assessment of the included studies

Items	SS Hellmann, 2015	M Yahabi, 2015	RH Jack, 2014	RR. Woods, 2018	C Woodhead, 2016	CL Price, 2010	E Guillaume, 2017	SN Vigod, 2011	C Renshaw, 2010	S Ouédraogo, 2014	S St-Jacques, 2013	LF Jensen, 2012	M Le, 2019	MN Zidar, 2015	LF Jensen, 2015	JT McDonald, 2017	EM Berens, 2014	LF Jensen, 2015	LF Jensen, 2015	C Pornet, 2010	SH Larsen, 2018	LF Jensen, 2012	R Wilf-Miron, 2011	D Roder, 2012	SM Tavasoli, 2018	B Vermeer, 2010	Dermot O'Reilly, 2012	DW Shin, 2020	JH Viuff, 2020
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	?	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6	?	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+
7	-	+	+	N	+	N	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+	-	+
13	?	+	+	N	-	N	N	?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
14	-	+	+	N	-	N	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
16	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
17	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
18	+	+	-	+	+	-	-	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+	+	+
19	-	-	-	-	-	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	?	-	-	-	-	-	-
20	+	+	?	N	N	?	?	+	N	+	+	N	+	+	N	+	+	N	N	?	N	N	N	+	?	+	N	+	N

** Yes = +; No = -; Don't know = ?; Not applicable = N*

Table S3: Summary of studies that reported the association between determinants and screening non-participation in a breast cancer screening program and studies included in the meta-analysis

Determinants	Studies reported the determinant	Studies included in the meta-analysis
Income level	M Vahabi [26], RH Jack [27], RR. Woods [28], E Guillaume [31], C Renshaw [33], S Ouédraogo [34], S St-Jacques [35], LF Jensen [36], M Le [37], JT McDonald [40], LF Jensen [43], C Pornet [44], SH Larsen [45], LF Jensen [46], R Wilf-Miron [47], SM Tavasoli [49], Shin DW [52]	M Vahabi [26], RH Jack [27], RR. Woods [28], E Guillaume [31], C Renshaw [33], S Ouédraogo [34], S St-Jacques [35], LF Jensen [36], M Le [37], JT McDonald [40], C Pornet [44], R Wilf-Miron [47], SM Tavasoli [49], Shin DW [52]
Age of women	RR. Woods [28], E Guillaume[31], C Renshaw [33], S Ouédraogo [34], S St-Jacques [35], LF Jensen [36], M Le [37], MN Zidar [38], LF Jensen [39], EM Berens [41], LF Jensen [42], C Pornet [44], SH Larsen [45], LF Jensen [46], R Wilf-Miron [47], SM Tavasoli [49], D O'Reilly [51], JH Viuff [53]	RR. Woods [28], E Guillaume[31], C Renshaw [33], S Ouédraogo [34], S St-Jacques [35], M Le [37], MN Zidar [38], LF Jensen [39], EM Berens [41], C Pornet [44], R Wilf-Miron [47], SM Tavasoli [49], D O'Reilly [51], JH Viuff [53]
Place of residence	M Vahabi [26], S Ouédraogo [34], S St-Jacques [35], JT McDonald [40], SM Tavasoli [49], D O'Reilly [51], DW Shin [52]	M Vahabi [26], S Ouédraogo [34], S St-Jacques [35], JT McDonald [40], SM Tavasoli [49], D O'Reilly [51], DW Shin [52]
Number of comorbidities	RR. Woods [28], SN Vigod [32], LF Jensen [39], LF Jensen [42], SH Larsen [45], SM Tavasoli [49], D O'Reilly [51], JH Viuff [53]	RR. Woods [28], SN Vigod [32], LF Jensen [39], SM Tavasoli [49], D O'Reilly [51], JH Viuff [53]
Education level	SN Vigod [32], LF Jensen [36], M Le [37], LF Jensen [39], JT McDonald [40], LF Jensen [42], D O'Reilly [51], SH Larsen [45]	SN Vigod [32], M Le [37], LF Jensen [39], JT McDonald [40], D O'Reilly [51]
Distance to an assigned screening unit	E Guillaume [31], S St-Jacques [35], LF Jensen [36], MN Zidar [38], JT McDonald [40], LF Jensen [46]	E Guillaume [31], S St-Jacques [35], LF Jensen [36], MN Zidar [38], JT McDonald [40]
Marital status	SN Vigod [32], LF Jensen [36], M Le [37], LF Jensen [39], JT McDonald [40], SH Larsen [45], LF Jensen [46], D O'Reilly [51]	SN Vigod [32], M Le [37], LF Jensen [39], JT McDonald [40], D O'Reilly [51]
Immigration status	LF Jensen [36], M Le [37], LF Jensen [39], SH Larsen [45], LF Jensen [46], B Vermeer [50]	LF Jensen [36], M Le [37], B Vermeer [50]
Physician's gender	M Vahabi [26], LF Jensen [46], SM Tavasoli [49]	M Vahabi [26], LF Jensen [46], SM Tavasoli [49]
Body mass index	SS Hellmann [25]	-
Mental disease	C Woodhead [29], SN Vigod [32]	-
Type of insurance	S Ouédraogo [34], C Pornet [44], R Wilf-Miron [47]	*
Car access	LF Jensen [36], D O'Reilly [51]	-

Determinants	Studies reported the determinant	Studies included in the meta-analysis
Travel time to the assigned screening unit	S Ouédraogo [34]	-
Net assest	M Le [37]	-
Employment status	LF Jensen [36] , M Le [37] , D O'Reilly [51]	*
Disability status	M Le [37] , DW Shin [52]	-
Self-assessed health status	M Vahabi [26] , LF Jensen [42] , D O'Reilly [51]	*
Residential ownership	D O'Reilly [51] , LF Jensen [36]	-
Social support	LF Jensen [43]	-
Cancer screening attending experience	RR. Woods [28] , CL Price [30] , SH Larsen [45]	*
Cancer screening invitation experience	C Renshaw [33]	-
Ethnicity	RH Jack [27] , CL Price [30] , C Renshaw [33] , D Roder [48]	*
Number of primary care visits	RR. Woods [28] , SN Vigod	-

-: Determinants that were reported by less than three studies.
**: Determinants that were measure or defined differently that not be able to be meta-analyzed.*

Table S4 Stratified analyses for the determinants of screening non-participation in breast cancer screening programs

Determinants	Variable	Stratified groups	Na	Non-participation %	OR	95%CI	I2%
Income Level (low vs. high (ref))	Type of invitation	Any invitation	10	31.2-49.7	1.22	1.10-1.35	99.7
		The first invitation	4	26.0-49.9	1.13	0.99-1.30	98.2
	Reference income group	Most affluent 20%	8	36.0-49.9	1.19	1.08-1.31	99.7
		Most affluent 30%	2	21.1-47.5	1.45	0.88-2.39	98.8
		Most affluent 50% and above	4	26.0-45.0	1.09	1.00-1.18	94.0
	Study region	North America	4	36.0-49.7	1.16	1.04-1.31	99.7
		Europe	8	21.1-49.9	1.23	1.05-1.45	99.9
		Asia	2	31.2-40.9	1.13	1.10-1.16	0.0
	Screening interval	24 months	12	21.1-49.9	1.17	1.08-1.27	99.6
		36 months	2	37.9-39.0	1.36	1.21-1.53	98.0
	Payment of screening	Free	12	21.1-49.9	1.22	1.12-1.34	99.7
		Co-payment	2	26.0-40.9	1.02	1.00-1.04	0.0
	Reminder for non-attenders	Yes	8	26.0-49.9	1.13	1.03-1.24	99.3
		No	6	21.1-47.6	1.29	1.11-1.49	99.8
	Adjusted estimate	Yes	6	31.2-49.9	1.13	1.11-1.16	0.0
		No	8	21.1-49.7	1.24	1.11-1.38	99.8
Woman's age (young vs. old (ref))	Type of invitation	Any invitation	12	19.0-50.8	1.09	0.99-1.19	99.8
		The first invitation	2	26.0-49.9	1.15	1.06-1.25	63.5
	Reference age group	60-64	1	24.9	1.30	1.04-1.62	-
		60-70	1	49.7	1.27	1.25-1.28	-
		65-70	6	20.2-50.8	0.99	0.91-1.08	99.6
		67-69	1	47.6	1.63	1.61-1.65	-
		70-74	5	19.0-49.9	1.06	0.98-1.15	90.0
	Study region	North America	3	47.6-49.7	1.29	1.01-1.65	99.9
		Europe	10	19.0-50.8	1.04	0.96-1.13	99.2
		Asia	1	31.2	1.00	1.00-1.01	-
	Screening interval	24 months	12	19.0-50.8	1.10	1.00-1.20	99.9
		36 months	2	24.9-37.9	1.08	0.79-1.49	87.7
	Payment of screening	Free	12	19.0-26.0	1.10	1.00-1.21	99.8
		Co-payment	2	20.2-50.8	1.04	0.81-1.34	99.1
	Reminder for non-attenders	Yes	7	19.0-50.8	1.14	1.04-1.24	99.8
		No	7	21.5-49.9	1.05	0.86-1.29	99.9
	Adjusted estimate	Yes	5	24.9-49.9	1.07	0.94-1.21	99.9
		No	9	19.0-50.8	1.07	1.01-1.29	86.6

Table S4 continued

Determinants	Variable	Stratified groups	Na	Non-participation %	OR	95%CI	I2%
Place of residence (urban vs. rural (ref))	Type of invitation	Any invitation	6	24.9-47.9	1.04	0.92-1.17	99.6
		The first invitation	1	45.0	0.83	0.79-0.87	-
	Study region	North America	4	36.0-47.9	0.91	0.80-1.03	99.6
		Europe	2	24.9-47.5	1.16	0.66-2.03	99.1
		Asia	1	40.9	1.14	1.10-1.17	-
	Screening interval	24 months	6	36.0-47.9	0.94	0.84-1.04	99.5
		36 months	1	24.9	1.54	1.45-1.64	-
	Payment of screening	Free	6	24.9-47.9	0.99	0.88-1.11	99.5
		Co-payment	1	40.9	1.14	1.10-1.17	-
	Reminder for non-attenders	Yes	3	45.0-47.9	0.83	0.82-0.84	0.0
		No	4	24.9-47.6	1.14	1.03-1.26	99.0
	Adjusted estimate	Yes	4	24.9-47.5	1.06	0.83-1.35	98.9
		No	3	36.0-47.9	0.94	0.81-1.09	99.8
Number of comorbidities (at least one vs. zero (ref))	Comorbidity measurement	CCI [b]	2	20.2-47.6	0.99	0.79-1.25	84.3
		ADG [c]	1	49.7	0.81	0.80-0.82	-
		Number of conditions	3	24.9-39.2	1.16	0.79-1.71	98.6
	Type of invitation	Any invitation	6	20.2-49.7	1.04	0.84-1.28	99.5
		The first invitation	0	-	-	-	-
	Study region	North America	3	39.2-49.7	0.86	0.78-0.95	97.0
		Europe	3	20.2-24.9	1.21	0.85-1.73	98.6
	Screening interval	24 months	5	20.2-49.7	1.05	0.83-1.33	99.6
		36 months	1	24.9	0.99	0.93-1.06	-
	Payment of screening	Free	6	20.2-49.7	1.04	0.84-1.28	99.5
		Co-payment	0	-	-	-	-
	Reminder for non-attenders	Yes	1	49.7	0.81	0.80-0.82	-
		No	5	20.2-47.6	1.10	0.81-1.48	99.3
	Adjusted estimate	Yes	3	20.2-39.2	1.01	0.94-1.08	5.3
		No	3	21.1-49.7	1.05	0.78-1.40	99.8

Table S4 continued

Determinants	Variable	Stratified groups	Na	Non-participation %	OR	95%CI	I2%
Education level (low vs. high (ref))	Type of invitation	Any invitation	3	21.1-39.2	1.08	0.98-1.17	71.3
		The first invitation	2	26.0-45.0	1.31	1.24-1.38	0.0
	Reference education level	< Secondary graduate	1	39.2	1.35	1.04-1.76	-
		≤ 10 years education	2	21.1-26.0	1.17	0.99-1.37	78.6
		< University graduate	2	24.9-45.0	1.15	0.88-1.49	96.7
	Study region	North America	2	39.2-45.0	1.31	1.24-1.39	0.0
		Europe	3	21.1-26.0	1.10	1.00-1.20	79.1
	Screening interval	24 months	4	21.1-45.0	1.24	1.08-1.42	90.8
		36 months	1	24.9	1.00	0.93-1.08	-
	Payment of screening	Free	4	21.1-45.0	1.15	1.02-1.31	92.3
		Co-payment	1	26.0	1.29	1.11-1.50	-
	Reminder for non-attenders	Yes	2	26.0-45.0	1.31	1.24-1.38	0.0
		No	3	21.1-39.2	1.08	0.98-1.17	71.3
	Adjusted estimate	Yes	3	24.9-45.0	1.19	0.96-1.48	93.6
		No	2	21.1-26.0	1.17	0.99-1.37	78.6
Distance to an assigned screening unit (large vs. small (ref))	Type of invitation	Any invitation	2	19.0-47.9	1.12	1.04-1.21	95.5
		The first invitation	3	45.0-49.9	1.24	0.84-1.83	95.7
	Reference distance level	≤ 2.5 km	1	47.9	1.06	1.05-1.07	-
		≤ 5 km	1	49.9	1.51	1.33-1.72	-
		≤ 10 km	1	45.0	1.02	0.93-1.12	-
		≤ 20 km	2	19.0-21.1	1.16	1.13-1.19	0.0
	Study region	North America	2	45.0-47.9	1.06	1.05-1.07	0.0
		Europe	3	19.0-49.9	1.25	1.09-1.42	87.5
	Screening interval	24 months	5	19.0-49.9	1.15	1.07-1.24	94.5
		36 months	0	-	-	-	-
	Payment of screening	Free	4	21.1-49.9	1.15	1.06-1.25	95.8
		Co-payment	1	19.0	1.14	1.03-1.25	-
	Reminder for non-attenders	Yes	3	45.0-49.9	1.17	0.98-1.39	93.3
		No	2	19.0-21.1	1.16	1.13-1.19	0.0
	Adjusted estimate	Yes	2	45.0-49.9	1.24	0.84-1.83	95.7
		No	3	19.0-47.9	1.12	1.04-1.21	95.5

Table S4 continued

Determinants	Variable	Stratified groups	Na	Non-participation %	OR	95%CI	I2%
Marital status (unmarried vs. Married (ref))	Type of invitation	Any invitation	3	24.9-39.2	1.73	1.09-2.76	97.5
		The first invitation	2	19.0-45.0	1.58	1.56-1.59	0.0
	Study region	North America	2	39.2-45.0	1.72	1.37-2.16	0.0
		Europe	3	19.0-26.0	1.66	1.24-2.22	99.7
	Screening interval	24 months	4	19.0-45.0	1.82	1.39-2.40	99.5
		36 months	1	24.9	1.26	1.11-1.43	-
	Payment of screening	Free	4	19.0-45.0	1.72	1.17-2.51	96.4
		Co-payment	1	26.0	1.58	1.56-1.59	-
	Reminder for non-attenders	Yes	2	26.0-45.0	1.58	1.56-1.59	0.0
		No	3	19.0-39.2	1.73	1.09-2.76	97.5
	Adjusted estimate	Yes	3	24.9-45.0	1.49	1.17-1.90	63.5
		No	2	19.0-26.0	1.89	1.32-2.70	99.8
Immigration status (immigrant vs. non-immigrant (ref))	Type of invitation	Any invitation	1	18.0-21.1	2.54	2.10-3.07	97.8
		The first invitation	2	26.0	2.81	2.76-2.85	0.0
	Study region	North America	0	-	-	-	-
		Europe	3	18.0-26.0	2.64	2.48-2.82	95.9
		Asia	0	-	-	-	-
	Screening interval	24 months	3	18.0-26.0	2.64	2.48-2.82	95.9
		36 months	0	-	-	-	-
	Payment of screening	Free	2	18.0-21.1	2.54	2.10-3.07	97.8
		Co-payment	1	26.0	2.81	2.76-2.85	-
	Reminder for non-attenders	Yes	2	18.0-26.0	2.80	2.77-2.83	0.0
		No	1	21.1	2.30	2.18-2.43	-
	Adjusted estimate	Yes	0	-	-	-	-
		No	3	18.0-26.0	2.64	2.48-2.82	95.9
Physician's gender (female vs. male (ref))	Type of invitation	Any invitation	2	36.0-47.6	1.56	1.33-1.85	99.1
		The first invitation	1	19.0	1.08	0.97-1.20	-
	Study region	North America	2	36.0-47.6	1.6	1.33-1.85	99.1
		Europe	1	19.0	1.08	0.97-1.20	-
	Screening interval	24 months	3	19.0-47.6	1.41	1.20-1.61	98.6
		36 months	0	-	-	-	-
	Payment of screening	Free	3	19.0-47.6	1.41	1.20-1.61	98.6
		Co-payment	0	-	-	-	-
	Reminder for non-attenders	Yes	0	-	-	-	-
		No	3	19.0-47.6	1.41	1.20-1.61	98.6
	Adjusted estimate	Yes	1	47.6	1.69	1.64-1.75	-
		No	2	19.0-36.0	1.25	0.94-1.67	96.4

a: Number of studies; b: Charlson Comorbidity Index; c: Aggregated Diagnosis Groups

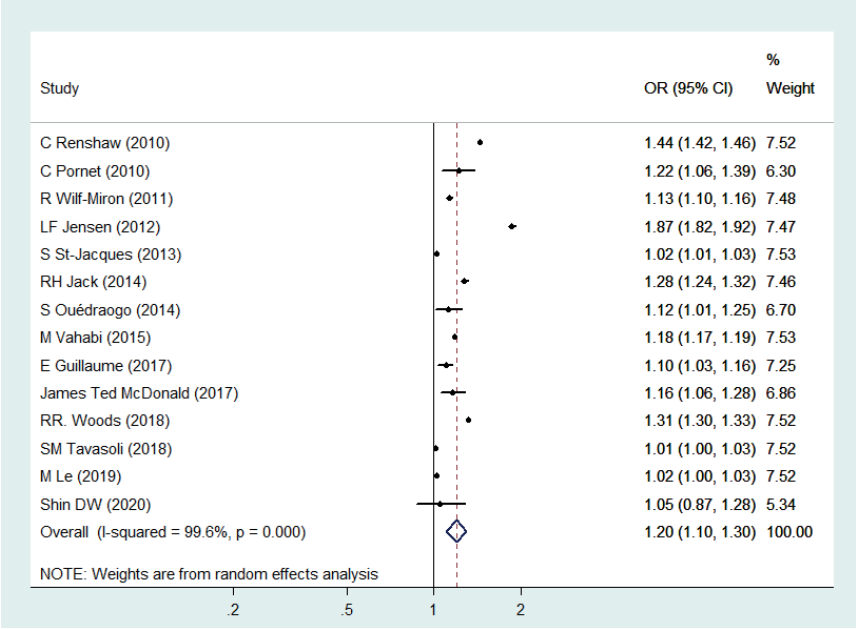

Figure S1 Forest plot of the association between income level (low vs. high) and screening non-participation of breast cancer screening programs.

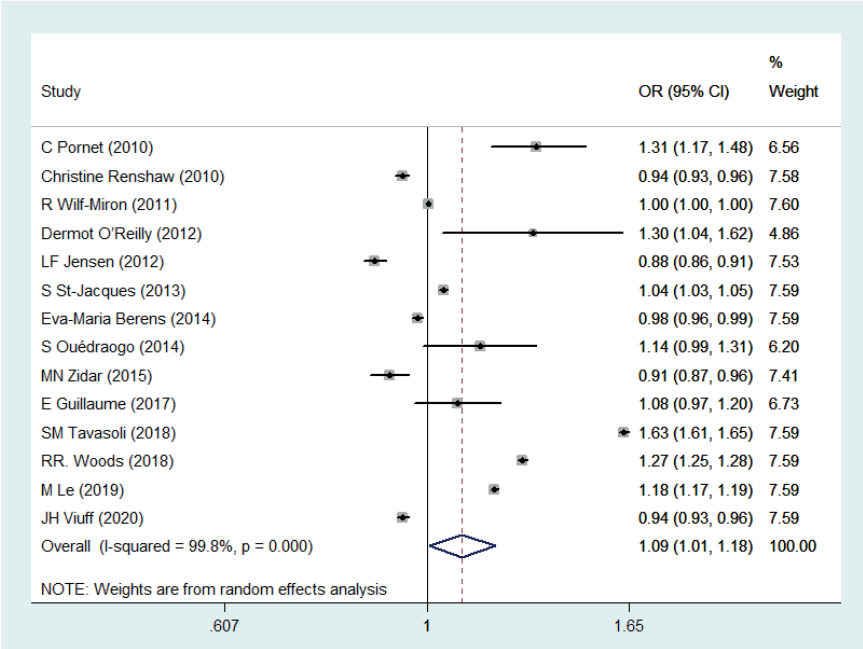

Figure S2 Forest plot of the association between women's age (young vs. old) and screening non-participation of breast cancer screening programs.

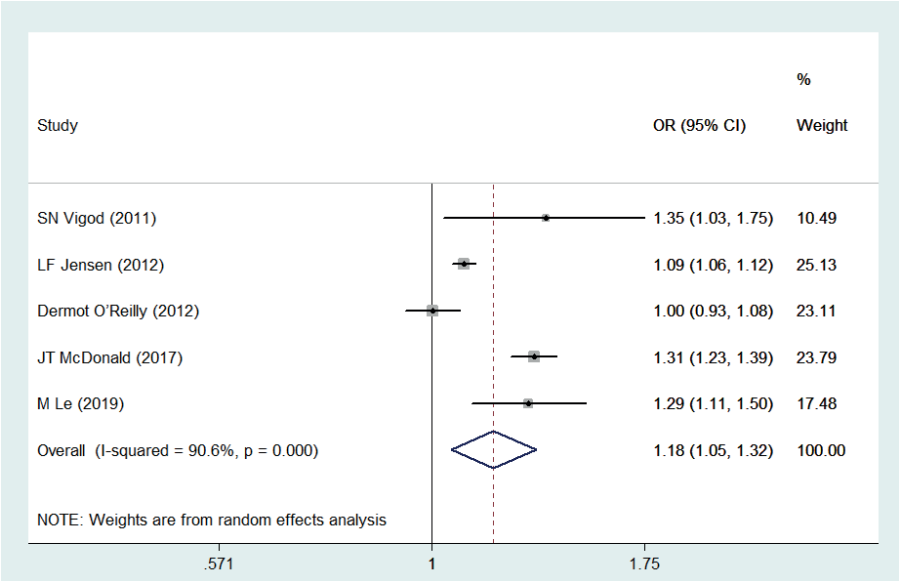

Figure S3 Forest plot of the association between education level (low vs. high) and screening non-participation of breast cancer screening programs.

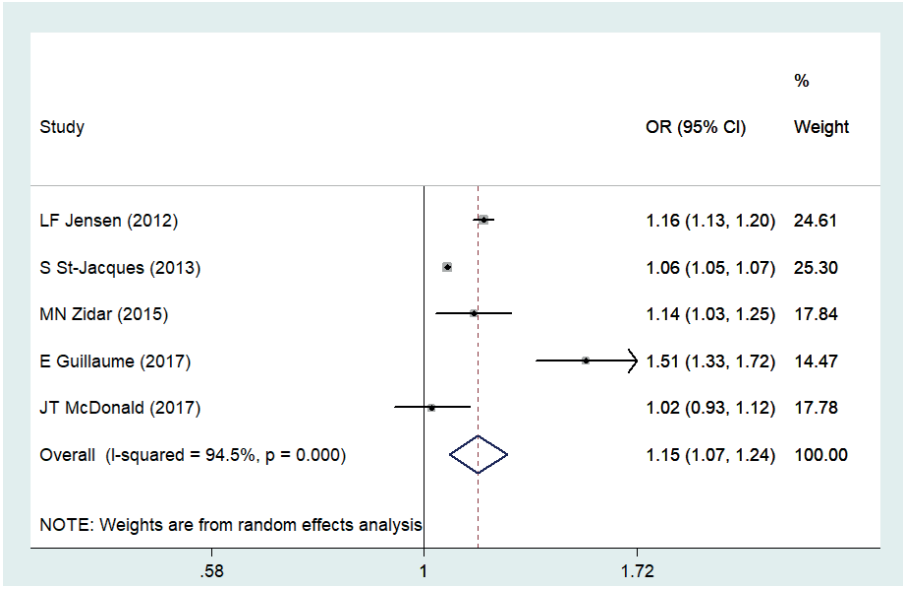

Figure S4 Forest plot of the association between women's living distance to an assigned screening unit (large vs. small) and screening non-participation of breast cancer screening programs.

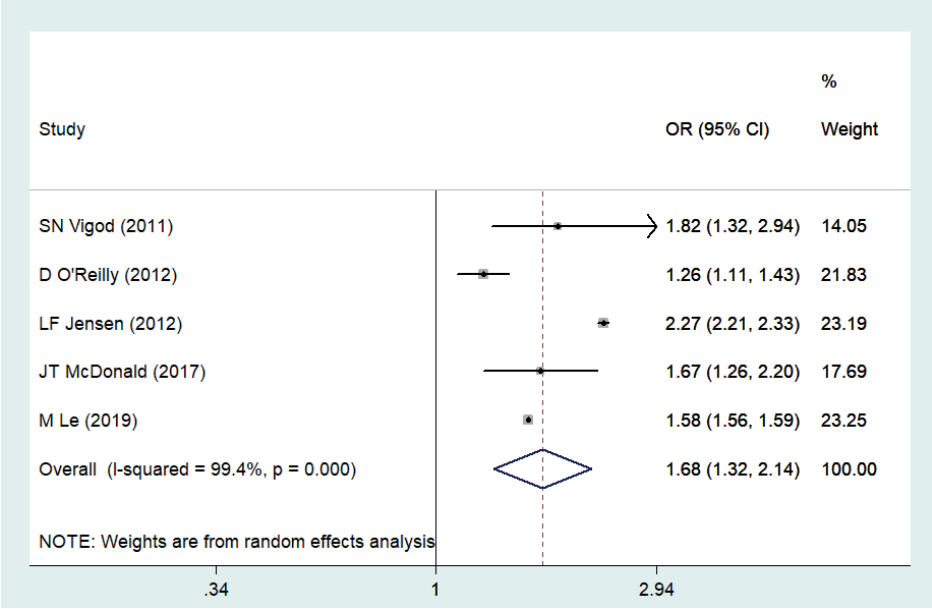

Figure S5 Forest plot of the association between women's marital status (unmarried vs. married) and screening non-participation of breast cancer screening programs.

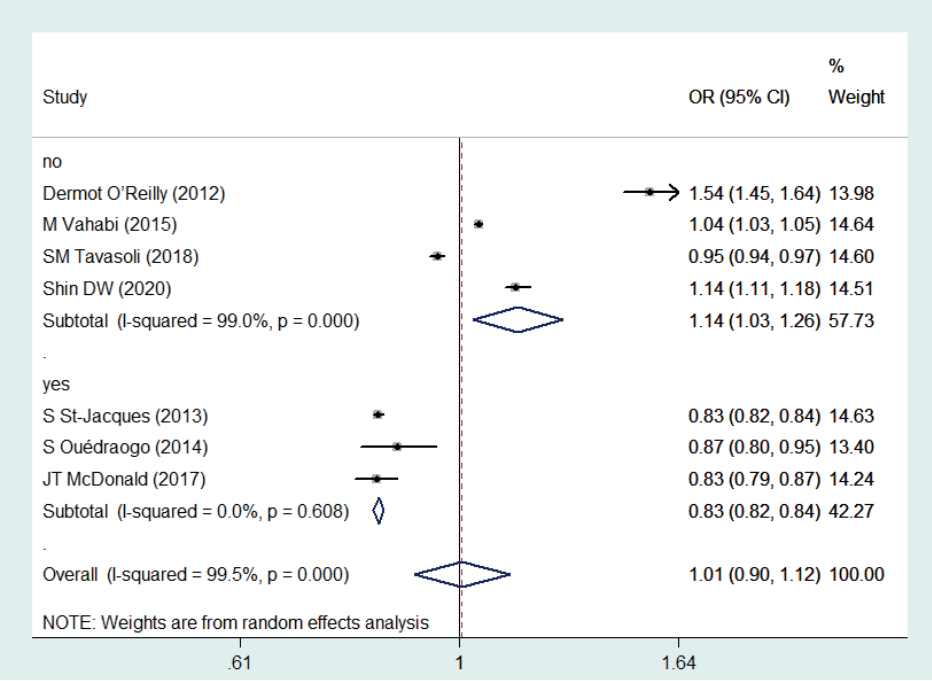

Figure S6 Forest plot of the association between place of residence (urban vs. rural) and screening non-participation of breast cancer screening programs stratified by reminders sent to non-attendees yes/no.

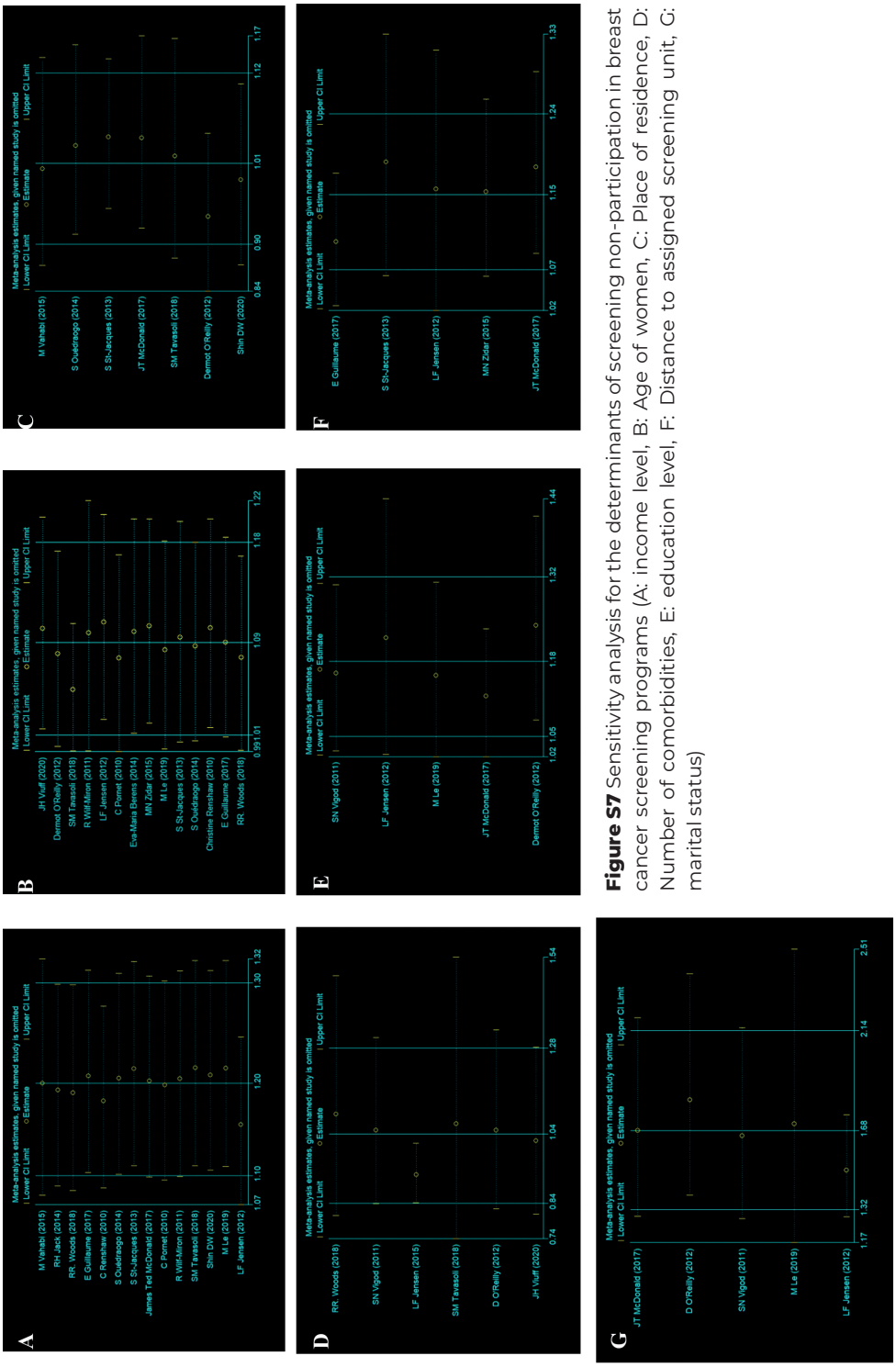

Figure S7 Sensitivity analysis for the determinants of screening non-participation in breast cancer screening programs (A: income level, B: Age of women, C: Place of residence, D: Number of comorbidities, E: education level, F: Distance to assigned screening unit, G: marital status)

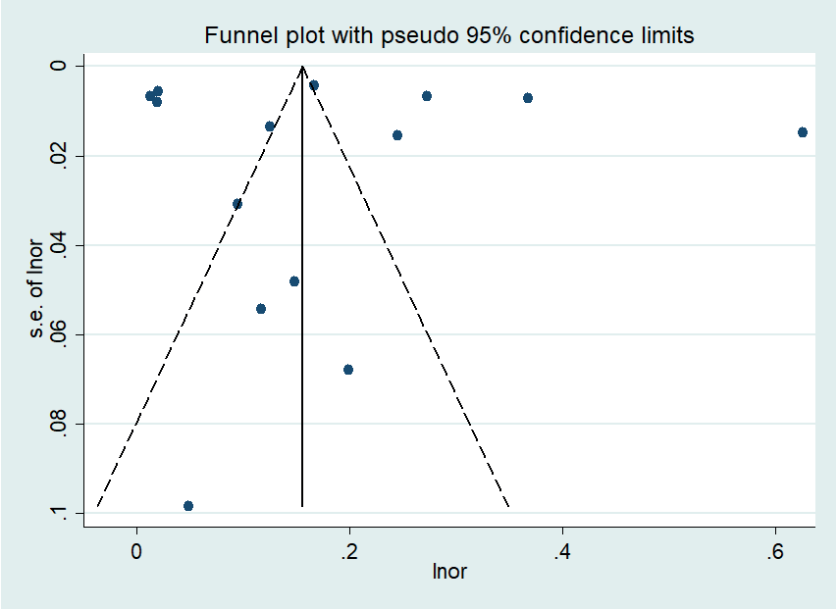

Figure S8 Funnel plot of the included studies on the association between women's income level and screening non-participation of breast cancer screening programs.

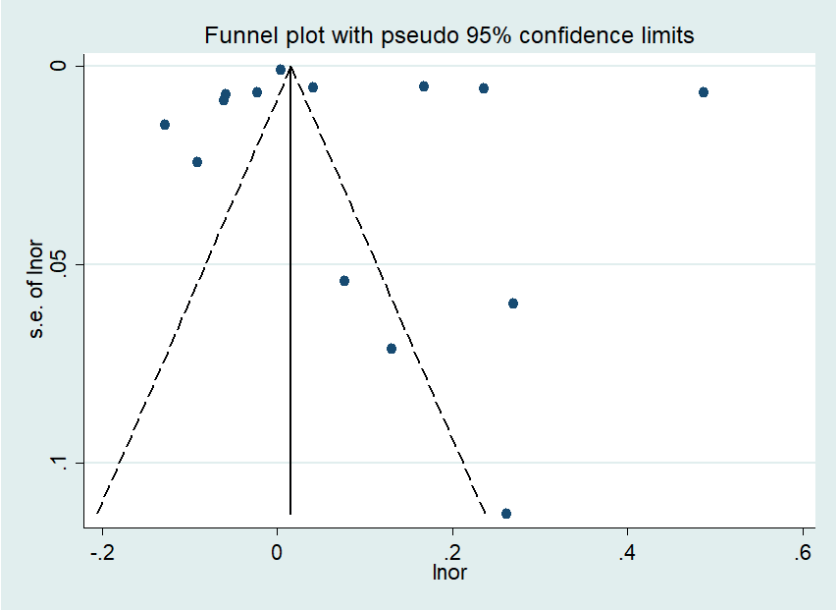

Figure S9 Funnel plot of the included studies on the association between women's age and screening non-participation of breast cancer screening programs.

Additional Information

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Authors' contributions: L. Ding: Conceptualization, systematic search strategy construction, paper selection and data extraction, data analysis, the original draft of manuscript writing and revision. **J. Wang:** Second reader for paper selection and data extraction, manuscript reviewing, and editing. **M.J.W. Greuter:** Conceptualization, Methodology, Writing- Reviewing, Editing, and Validation. **G.H. de Bock:** Supervision, Conceptualization, Methodology, Writing- Reviewing, Editing, and Validation. **M. Goossens:** Writing- Reviewing and Editing, Validation. **G. Van Hal**: Conceptualization, Methodology, Writing- Reviewing, Editing, and Validation.

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CHAPTER 5

COVERAGE DETERMINANTS OF BREAST CANCER SCREENING IN FLANDERS: AN EVALUATION OF THE PAST DECADE

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Abstract

Background Breast cancer (BC) is the most common cancer in women in the developed world. In order to find developing cancers in an early stage, BC screening is commonly used. In Flanders, screening is performed in and outside an organized breast cancer screening program (BCSP). However, the determinants of BC screening coverage for both screening strategies are yet unknown.

Objective To assess the determinants of BC screening coverage in Flanders.

Methods Reimbursement data were used to attribute a screening status to each woman in the target population for the years 2008-2016. Yearly coverage data were categorized as screening inside or outside BCSP or no screening. Data were clustered by municipality level. A generalized linear equation model was used to assess the determinants of screening type.

Results Over all years and municipalities, the median screening coverage rate inside and outside BCSP was 48.40% (IQR: 41.50-54.40%) and 14.10% (IQR: 9.80-19.80%) respectively. A higher coverage rate outside BSCP was statistically significantly ($P < 0.001$) associated with more crowded households (OR: 3.797, 95% CI: 3.199-4.508), younger age, higher population densities (OR: 2.528, 95% CI: 2.455-2.606), a lower proportion of unemployed job seekers (OR: 0.641, 95% CI: 0.624-0.658) and lower use of dental care (OR: 0.969, 95% CI: 0.967-0.972).

Conclusion Coverage rate of BC screening is not optimal in Flanders. Women with low SES that are characterized by younger age, living in a high population density area, living in crowded households, or having low dental care are less likely to be screened for BC in Flanders. If screened, they are more likely to be screened outside the BCSP.

Keywords: Breast Neoplasms; Mammography; Mass Screening; Coverage rate; Social Determinants of Health

Background

Belgium is among the countries with the highest female breast cancer (BC) incidence and mortality worldwide.[1] In 2018, the age-standardized BC incidence and mortality rate of Belgium women were 113.2/100,000 and 22.2/100,000 person-years, respectively, which is higher than the estimate for the whole Western European region (92.6 and 15.5/100,000 person-years, respectively).[1, 2] While sufficient evidence has indicated that mammography screening has the potential to initiate early diagnosis and treatment for BC and lower BC mortality, the effect of mammography screening relies on the degree to which women participate in screening.[3]

In most of the high income countries, women are recommended to participate in an organized BC screening program (BCSP), where quality is warranted by systematic quality control measures.[4] Outside this program, with the aim to screen more of the eligible women, spontaneous screening is also endorsed in some countries, such as in Belgium[5], France[6] and Switzerland[7]. The coverage of BC screening, defined as the percentage of screened women in the total eligible population within the specific interval of routine screening[8], is an important indicator for the evaluation of the effectiveness of screening.[4, 9] However, the average coverage rate in 2016 across OECD countries was only 57.4%[10]. As for Flanders, the coverage rate of BCSP in 2017 was only 49% and 13% was screened outside the BCSP.[11]

Many factors have previously been shown to be associated with a reduced coverage level of BCSP. A systematic review summarized that the barriers to BC screening fell into three categories: 1) health care system level barriers, such as lack of health care providers and economic barriers; 2) social barriers, such as lack of social support and cultural norms opposed to BC screening;, and 3) individual level barriers, such as lack of cancer knowledge and beliefs, negative expectations of screening, and distrust of the medical system.[12] However in this review, the majority of the included studies relied on self-reported data, studies with random and convenience samples were pooled, and evidence was only qualitatively synthesized. Many other studies have also provided quantitative evidence on these hampering factors. Among them, economic related barriers were the most commonly studied factors and results showed that low income[13], crowded housing condition[14], unemployment[15] and residing in social-economically deprived areas[16] are predictors of a lower BC screening coverage rate. Lack of a regular health care provider is associated with a reduced coverage rate of screening both inside[17] and outside a BCSP.[7] Other individual level characteristics include residential instability[18], being an immigrant[19], physical disability[20], and having one or more chronic diseases[21]. Only a relatively small amount of studies are dedicated to exploration of the determinants of screening outside a

BCSP. Regular visits to a gynecologist, being employed and low esteem of the quality of the population screening program are associated with an increased attendance to screening outside a BCSP.[6, 7, 22] However, these studies only depend on self-reported data from health surveys or focus group discussions.

There is a paucity of studies that have investigated the determinants of screening coverage in a setting that has BC screening in and outside BCSP. The aim of this study therefore was to evaluate the factors associated with the coverage rate of mammography screening and factors that contribute to women's choice of screening in and outside the BCSP using municipality level aggregated data.

Methods

Screening in Flanders

Flanders, the most populated region of Belgium, established a BCSP for women aged 50-69 in 2001.[5] The organization and implementation of mammography screening in and outside the BCSP in Flanders have been described in detail elsewhere.[5, 23, 24] Briefly, in BCSP, every two years, eligible women aged 50-69 are actively recruited through a personalized invitation letter sent by the Center for Cancer Detection in Flanders with a fixed time and place for a digital mammography screening fully and directly paid by the health insurance system in Flanders. The Flemish program follows the European quality assurance guidelines.[9] Mammography screening outside the context of the BCSP can be accessed by a referral from a general practitioner (GP) or a gynecologist, is not fully covered by health insurance,[5] and does not systematically include quality-control activities (e.g. double reading).[5] Since 2016, women who received reimbursement for mammography in the last two years from the health insurance or have been diagnosed with BC in the last 10 years in the Flemish health care system are not invited for the population screening program.

Data description

Municipality level screening coverage in 2008-2016 was calculated using data from the Center for Cancer Detection in Flanders.[25] Municipalities that have no missing values of the number of screened and non-screened women were included in the study. Independent variables at the municipality level of 2008-2016 were derived from the database of the Flemish provincial authorities and linked to data of the screening coverage. We included only the variables that were publicly available in order to reduce the bias that may be induced by the selection of variables.[26]

Privacy considerations

Privacy was warranted since only aggregated data were available at municipality level and for municipalities with less than 5 screened women overall or in one of the four age groups (50-54, 55-59, 60-64, and 65-69), a missing value was used.

Main outcome

The main outcome of our analysis was the screening coverage rate inside and outside the BCSP from 2008 to 2016. The coverage rate was presented overall as a median value over all years and municipalities and stratified by age groups and the two screening strategies.

Determinants considered

For an overview of the variables considered in the analysis, see Table 1. *Number of residents and population density* were defined as the total number of residents and the number of residents per km^2 per municipality, respectively. *Natural balance* was defined as the natural growth per 1,000 residents per municipality. *Residential stability* was indicated by the percentage of residents having the same address as the year before. *Non-Belgian nationality* was defined as the percentage of residents without a Belgian nationality per municipality. The socioeconomic status (SES) of residents was characterized by the following four proxy variables: (1) *Average household size* was defined as the average number of residents per households as a proxy for crowded housing conditions. (2) *Women with equivalent living wages* was defined as the percentage of women with equivalent living wages which is the minimum income awarded by the social welfare center. (3) *Share of borrowers with at least one overdue loan* was defined as the percentage of borrowers with at least one overdue loan per municipality where a high percentage was considered as a proxy for poverty; and (4) *Job seekers* were defined as the percentage of unemployed residents with waiting allowance or bridging allowance per municipality. Health status was indicated by residents aged 18-64 with *physical disability* or *status of diabetes*, and defined as the percentage of handicapped residents aged 18-64 and the percentage of residents with diabetes recognized by the health insurance system, respectively. Healthy behavior was indicated by *dental visit* defined as the percentage of residents having at least 2 visits at the dentist in 2 different years within a period of 3 calendar years per municipality.

Statistical analysis

Median value and interquartile range (IQR): p25-p75 were calculated for all continuous variables which were not normally distributed. The annual screening coverage rate inside and outside the BCSP was calculated as a median value over all years and municipalities and presented overall and stratified by four age groups: 50-54, 55-59, 60-64, and 65-69. To evaluate which determinants were related to the annual coverage of the two screening strategies, a logistic regression model with generalized estimating equations (GEE) was

constructed to account for the correlation of repeated measurements of municipality level screening coverage rate and social demographic parameters. In the GEE model, the dependent variable was the municipality level coverage rate and the independent variables were the municipality level social demographic parameters as given in Table 1. A binary variable that indicated the type of screening strategy that the coverage rate referred to was provided and used as an independent variable. Odds ratios (OR) were reported with 95% confidence interval (CI). The effect of social demographic parameters was investigated by assessing a two-way interaction between the two screening strategies and the significant independent variables. All statistical analyses were performed using R version 3.6.0, and a two-sided $P < 0.05$ was considered statistically significant.

Results

We included 295 of the 308 municipalities in Flanders that reported full data of the number of screened women of the two screening strategies in all age groups in 2008-2016. The median percentages of all included social demographic parameters over all years and municipalities are shown in table 1.The overall median coverage of all years and municipalities of both screening strategies combined was 60.90%. The median coverage rates of all years and municipalities inside and outside the BCSP were 48.40% (IQR: 41.50-54.40%) and 14.10% (IQR: 9.80-19.80%) respectively, table 2. The median coverage of screening outside the BCSP decreased from 2008 to 2016, especially in the youngest age group, while an increase of screening coverage inside the BCSP was seen in all age groups, Figure 1.

Table 1 Social demographic parameters of Flanders per municipality in the period 2008-2016. In total 295 municipalities were included

	Median (P25-P75)
Population and households	
number of residents (10^5 residents)	0.15 (0.10-0.22)
population density (1000 residents per km^2)	0.41 (0.27-0.66)
natural balance (per 1000 residents)	0.86 (-0.76-2.43)
same address as last year (compared to all residents)%	92.50 (91.40-93.30)
non-Belgian nationality (compared to all residents)%	3.30 (2.10-6.00)
average household size	2.44 (2.37-2.51)
Welfare and poverty (%)	
women with equivalent living wages (compared to all women residents)	0.26 (0.18-0.41)
share of borrowers with at least one overdue loan (compared to all borrowers)	3.00 (2.50-3.80)
job seekers (compared to all residents)%	1.80 (1.40-2.20)
Health and handicap (%)	
person with physical disability18-64y (compared to all residents in 18-64y)	1.96 (1.57-2.58)
diabetes (compared to all residents)	5.10 (4.60-5.60)
dental visit (compared to all residents)	54.50 (51.30-57.70)

Table 2 Median screening coverage (P25-P27) in Flanders

	Screening coverage (%): Median (P25-P75)	
	Population BC screening	**Non-population BC screening**
Overall	48.40 (41.50-54.40)	14.10 (9.80-19.80)
Age group		
50-54 year	45.40 (37.50-51.30)	17.50 (13.00-24.10)
55-59 year	50.10 (42.80-56.10)	14.30 (10.00-20.50)
60-64 year	50.10 (43.60-56.20)	13.50 (9.30-18.70)
65-69 year	47.80 (42.40-53.40)	11.40 (8.20-16.00)

From the univariate analysis it followed that significantly less women were screened outside the BCSP than inside the BCSP (OR: 0.184, 95% CI: 0.180-0.189). The probability of being screened in or outside the BCSP was positively associated with the average household size (OR: 1.282, 95% CI: 1.138-1.444), while negatively associated with the percentage of women with equivalent living wages (OR: 0.899, 95% CI: 0.855-0.945), the percentage of unemployed job seekers (OR: 0.961, 95% CI: 0.936-0.987) and population density (OR: 0.918, 95% CI: 0.888-0.949). (Table 3). After the adjustment for social demographic parameters in the multivariate analysis, the probability of being screened inside or outside the BCSP was only negatively associated with average household size (OR: 0.894, 95% CI: 0.809-0.988), population density (OR: 0.929, 95% CI: 0.906-0.952), and diabetes prevalence (OR: 0.964, 95% CI: 0.952-0.976) whereas positively associated with the percentage of unemployed job seekers (OR: 1.073, 95% CI: 1.051-1.095), and the percentage of residents with proper dental care (OR: 1.005, 95% CI: 1.003-1.007). (Table 4).

Contrary to the BCSP, the probability of being screened outside the BCSP was positively associated with being in a younger age group, a high population density (OR: 2.528, 95% CI: 2.455-2.606), and a larger households size (OR: 3.797, 95% CI: 3.199-4.508), and negatively associated with the diabetes prevalence (OR: 0.942, 95% CI: 0.921-0.962), the percentage of unemployed job seekers (OR: 0.641, 95% CI: 0.624-0.658) and the percentage of residents with proper dental care (OR: 0.969, 95% CI: 0.967-0.972). (Table 4).

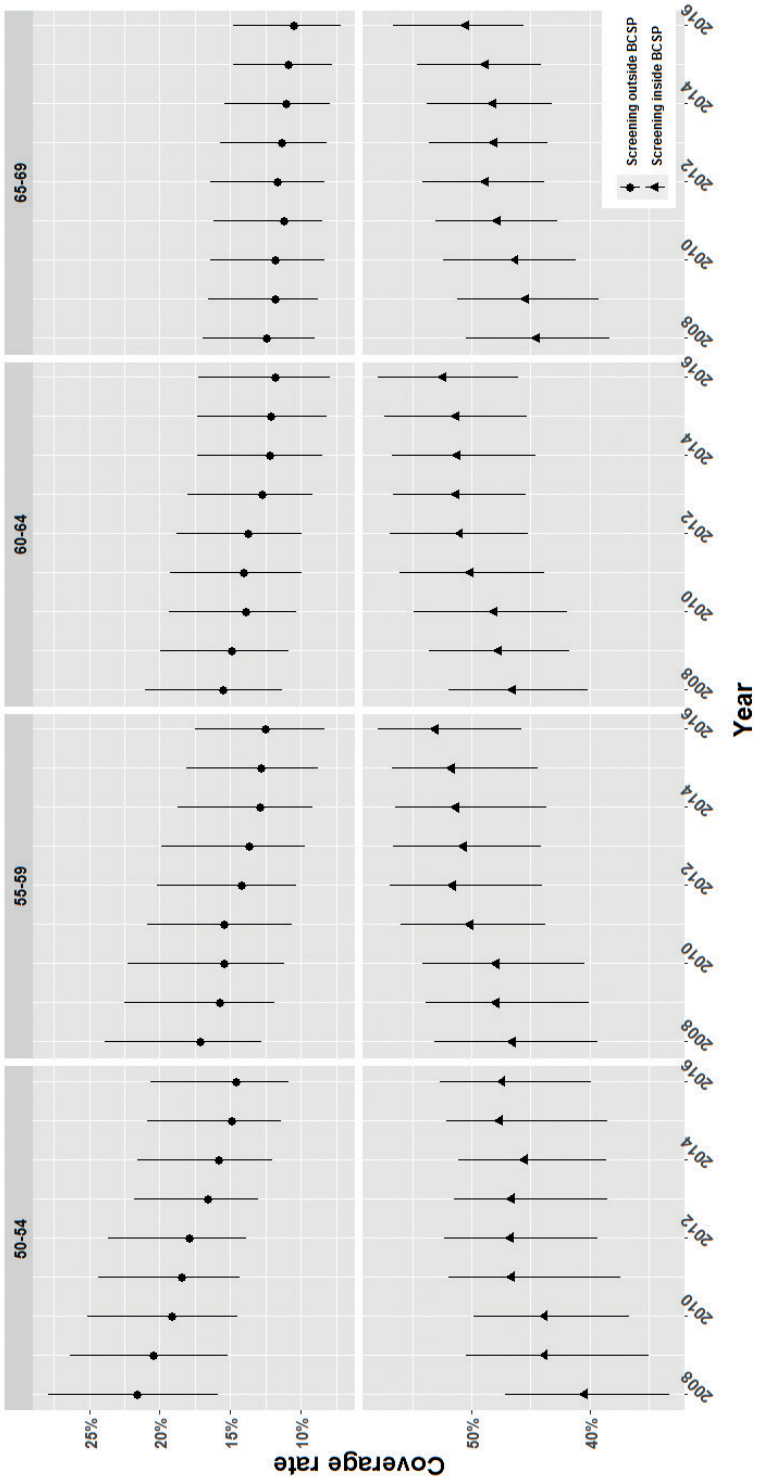

Figure 1 Median (P25-P75) screening coverage rate of 295 municipalities by age groups in 2008–2016

Table 3 Univariate analysis of the determinants of screening in or outside the population BC screening

Variable	Crude OR (95% CI)	*P* value
Year	1.002 (0.996-1.008)	0.534
Age group		<0.001
50-54 year	ref	
55-59 year	1.034 (0.993-1.077)	
60-64 year	1.014 (0.973-1.057)	
65-69 year	0.933 (0.894-0.973)	
BC screening		<0.001
Population BC screening	ref	
Non-population BC screening	0.184 (0.180-0.189)	
Population and households		
number of residents (10^5 residents)	0.962 (0.941-0.983)	<0.001
population density (1000 residents per km^2)	0.918 (0.888-0.949)	<0.001
natural balance (per 1000 residents)	0.996 (0.990-1.002)	0.194
same address as last year (compared to all residents)	1.024 (1.013-1.035)	<0.001
non-Belgian nationality (compared to all residents)	0.996 (0.993-0.999)	0.016
average household size	1.282 (1.138-1.444)	<0.001
Welfare and poverty		
women with equivalent living wages (compared to all women)	0.899 (0.855-0.945)	<0.001
share of borrowers with at least one overdue loan (compared to all borrowers)	0.970 (0.958-0.982)	<0.001
job seekers (compared to all residents)	0.961 (0.936-0.987)	0.004
Health and handicap		
physical disability18-64y (compared to all residents of 18-64y)	1.003 (0.986-1.021)	0.701
diabetes (compared to all residents)	0.972 (0.954-0.991)	0.003
dental visit (compared to all residents)	1.009 (1.006-1.012)	<0.001

Table 4 Multivariable analysis of the determinants of screening in or outside the population BC screening

Variable	Model 1[a]		Model 2[b]	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age group		<0.001		<0.001
50-54 year	ref		ref	
55-59 year	1.039 (1.015-1.065)		1.207 (1.179-1.235)	
60-64 year	1.018 (0.994-1.042)		1.217 (1.190-1.244)	
65-69 year	0.928 (0.907-0.949)		1.142 (1.117-1.167)	
BC screening		<0.001		<0.001
Population BC screening	ref		ref	
Non-population BC screening	0.224 (0.220-0.229)		0.303 (0.295-0.312)	
Population and households				
number of residents (10^5 residents)	0.983 (0.965-1.001)	0.059	0.996 (0.985-1.007)	0.444
population density (1000 residents per km²)	0.929 (0.906-0.952)	<0.001	0.647 (0.634-0.660)	<0.001
same address as last year (compared to all residents)	1.008 (0.998-1.018)	0.123	1.005 (0.995-1.015)	0.309
non-Belgian nationality (compared to all residents)	1.0005 (0.9984-1.0025)	0.654	0.9997 (0.9982-1.0012)	0.719
average household size	0.894 (0.809-0.988)	0.028	0.580 (0.522-0.645)	<0.001
Welfare and poverty				
women with equivalent living wages (compared to all women)	0.972 (0.934-1.012)	0.164	0.987 (0.947-1.029)	0.532
share of borrowers with at least one overdue loan (compared to all borrowers)	0.989 (0.976-1.002)	0.092	0.989 (0.978-1.001)	0.067
job seekers (compared to all residents)	1.073 (1.051-1.095)	<0.001	1.250 (1.226-1.273)	<0.001
Health can handicap				
diabetes (compared to all residents)	0.964 (0.952-0.976)	<0.001	0.985 (0.973-0.997)	0.016
dental visit (compared to all residents)	1.005 (1.003-1.007)	<0.001	1.016 (1.015-1.018)	<0.001
Interaction terms				
age group × BC screening				<0.001
NPS × 50-54 year			ref	
NPS × 55-59 year			0.668 (0.642-0.694)	
NPS × 60-64 year			0.612 (0.589-0.636)	
NPS × 65-69 year			0.554 (0.533-0.576)	
NPS × population density			2.528 (2.455-2.606)	<0.001
NPS × average household size			3.797 (3.199-4.508)	<0.001
NPS × job seekers			0.641 (0.624-0.658)	<0.001
NPS × status of diabetes			0.942 (0.921-0.962)	<0.001
NPS × dental visit			0.969 (0.967-0.972)	<0.001

[a] *model 1: multivariable regression model including all significant covariates of the univariate regression.*
[b] *model 2: multivariable regression model including two-way interaction terms between screening strategies and the significant covariates in model 1.*
NPS = Non-population BC screening

Discussion

In the present study, we assessed the coverage determinants of screening inside and outside the BCSP in Flanders. A median 48.4% of women aged 50-69 are screened by the BCSP which is significantly higher than the 14.1% of women screened outside the program. Working women in younger age group (50-54 years of age), and women living in crowded households with low dental care go less frequently to the screening, and if they go, they tend to be screened more frequently outside the context of the BCSP.

The total median coverage rate of 60.90% of screening inside and outside the BCSP is within the range of coverage levels of European countries (average: 48.2% (range: 19.4-88.9%)).[27] The median coverage rate of the BCSP in Flanders of 48.4% is close to the coverage rate of the BCSP in countries such as France (52.8%)[6] and Switzerland (46.7%)[7, 27] and higher than in Serbia (38.0%).[28] In these three countries there is screening in and outside the context of the BCSP. However, it is much lower than the coverage rate of the BCSP in some western and northern European countries like the United Kingdom (78.0%), the Netherlands (78.5%), and Norway (72.1%)[27] where only the BCSP is endorsed as the population screening strategy.

From 2006 to 2016, the coverage rate of BCSP increased while the coverage rate outside the BCSP decreased . This effect might be explained by public health campaigns via mass media and community education programs[24, 29], which increased the visibility and awareness of BCSP for the target population and their doctors.[29, 30] A decrease in screening coverage rate was observed from 17.50% to 11.40% for the individuals from age 50-54 to 65-69 years old in the screening outside the BCSP, whereas this pattern was not observed for the individuals in the BCSP. A similar pattern is also observed in countries like France[6, 31] and the United States of America[32] where both screening strategies are provided in large scale. A potential explanation can be that older women are more likely to attend the relatively fixed time and place of the BCSP than younger working women.

We found that living in crowded households, living in an area with high population density, and having a low dental care are associated with a lower probability of being screened. These three characteristics are all indicators for a low SES. People living in areas with a high population density tend to have a lower SES.[33] People living in crowded household are more likely to fall into income poverty.[34] As dental care is not fully covered by the health insurance system in Flanders[35], a low dental care indicates a lower SES.[36] Similar associations are also available in the literature regarding the increased BCSP coverage and increased dental care[19], less crowded household condition[14], and decreased population density.[37]

Interestingly, women that are characterized by living in an area with high population density, living in a more crowded households, or having a low dental care tend to go more frequently for screening outside the BCSP. The reverse SES gradient in the use of screening in and outside BCSP was also seen in other settings where both screening strategies coexist.[6, 7, 37] An explanation for this phenomenon is that women with a higher SES are more likely to have a higher level of health literacy.[38] For these women, information regarding the importance of mammography screening and the systematic quality control is more likely to motivate them to participate in the BCSP.[5,29] Another explanation is that poor employed women could have less flexible working time, which can conflict with the fixed working time of organized screening units.[6, 7, 37, 39] It has also been mentioned that areas with a higher population density have a lower population BC screening capacity (defined as the number of mammography facilities per 10,000 women)[40] and that in these areas there are more private clinics for opportunistic screening.[37] As a lower capacity of screening units can induce a longer waiting time and therefore a lower satisfaction of screening experience[5], low SES women living in these areas might be more likely to have negative screening experience and as a consequence prefer to go for screening outside the BCSP.[22]

The strength of this study is that we examined determinants of coverage rate of screening in and outside the BCSP with longitudinal administrative data instead of self-reported screening uptake, which may induce recall bias. For that, regular collected and maintained administrative data of screening coverage outside the BCSP were applied. This enabled us to evaluate the determinants of the two coexisting screening strategies for BC and to better understand which further efforts are needed to improve the coverage of the BCSP in Flanders. However, our study had some limitations as well. First, a limitation of this study was the use of aggregated data, which reduced the options to evaluate correlation structures in the data.[41] Similarly, due to the aggregated data, a variation of coverage rate and the associated determinants within a municipality can be concealed. However, the association between the determinants and screening uptake in our study is consistent with other studies that applied neighborhood or individual level factors.[13, 18, 19] Second, proxy variables for SES were applied instead of income which can directly characterize SES of women. However, the proxy variables used are commonly applied and the magnitude and direction of the association between variables is consistent with the literature.[6, 14, 18]

Conclusion

A sizeable part of women attend screening outside the BCSP in Flanders. Women with low SES that are characterized by younger age, living in a high population density area, living in crowded households, or having low dental care, go less frequently to screening. If they go to screening, they are more likely to be screened outside the BCSP. Further efforts targeted on this group of women are needed to improve the coverage rate of the BCSP in Flanders.

Additional Information

Ethics approval and consent to participate: Not applicable.

Consent for publication: All authors have approved the manuscript and agree with this submission.

Availability of data and material: Breast cancer screening coverage dataset is available at https://bevolkingsonderzoek.incijfers.be/, variables regarding the determinants of screening coverage can be requested by contacting the Center for Cancer Detection in Flanders at www.bevolkingsonderzoek.be.

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CHAPTER 6

THE ROLE OF SOCIODEMOGRAPHIC FACTORS IN THE COVERAGE OF BREAST CANCER SCREENING: INSIGHTS FROM A QUANTILE REGRESSION ANALYSIS

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Abstract

Background In Flanders, breast cancer (BC) screening is performed in a population-based breast cancer screening program (BCSP), as well as in an opportunistic setting. Women with different socio-demographic characteristics are not equally covered by BC screening.

Objective To evaluate the role of socio-demographic characteristics on the extreme (low and high) levels of BC screening coverage.

Methods The coverage rates of 2017 of BCSP and opportunistic screening at the neighborhood level were linked to socio-demographic data of 2017. The association between the socio-demographic characteristics and the coverage rates of BCSP and opportunistic screening was evaluated per quantile of coverage using multivariable quantile regression models, with specific attention to the lower 10th and upper 90th quantiles.

Results The median coverage in the BCSP was 50%, 33.5% in the 10^{th} quantile, and 64.5% in the 90^{th} quantile. The median coverage of the opportunistic screening was 12%, 4.2% and 24.8% in the 10^{th} and 90^{th} quantile, respectively. A lower coverage of BCSP was found in neighborhoods with more foreign residents and larger average household size, being indicators for lower socioeconomic status (SES). However a higher average personal annual income, being an indicator for higher SES, was also found in neighborhoods with lower coverage in the BCSP. For these neighborhoods that have the relatively low and high SES, the negative association between the percentage of foreign residents, average household size, and average personal annual income and the coverage in the BCSP had the smallest regression coefficient and 95% confidence interval (CI) values -0.75, (95%CI: -0.85, -0.65), -13.59, (95%CI: -15.81, -11.37), and -1.05,(95%CI: -1.18, -0.92), respectively in the 10^{th} quantile. The neighborhoods with the higher coverage of opportunistic screening had a relatively higher average personal annual income, with the largest regression coefficient 1.72, (95%CI: 1.59, 1.85), in the 90^{th} quantile.

Conclusions Women from the relatively low and high SES neighborhoods tend to participate less in the BCSP, where women with relatively high SES tend to participate more in the opportunistic screening. For women from the low SES neighborhoods, tailored interventions are needed to improve the BCSP.

Key words Breast cancer, mammography screening, coverage, social inequality, determinant, quantile regression.

Introduction

Worldwide breast cancer has been the most common cause of cancer death in women.[1] In 2018 the global age-standardized incidence and mortality rates of breast cancer were 54.4 and 11.6 per 100,000 women, respectively.[1] Randomized controlled trials have confirmed that mammography screening can reduce the risk of breast cancer mortality by 20% for women aged 50-70 who attend this screening.[2] The European guideline for quality assurance in breast cancer screening and diagnosis suggest to strive for 70% screening coverage in order to have a significant effect on breast cancer burden in the population. However, this percentage is not obtained in many countries where a breast cancer screening program (BCSP) has been established. In Europe, the mean screening coverage is about 50% (range 28%-92%), meaning that a large proportion of women who are eligible for screening are not covered by the population breast cancer screening programs. This does not mean these women do not receive any form of BC screening, since opportunistic BC screening exists in many countries.[3]

To understand the reasons for this low coverage, several studies assessed the determinants of screening coverage. The main reported determinants of low screening coverage were related to low socioeconomic status (SES): lower income level, having an immigrant background, being a single parent.[4-7] The conclusions of these studies are mainly derived from linear regression modeling, in which the change in the mean coverage is estimated as a function of the explanatory variables. However, the determinants of screening coverage for women who have the most extreme levels of screening coverage are more of interest to policymakers than the average women. In order to improve the screening coverage of the BCSP, it is important to know the characteristics of the women with the lowest coverage in the BCSP, as well as those of the women with the highest coverage in the opportunistic screening. These insights can assist policy makers to implement specific actions to increase the screening coverage of the BCSP, especially for those groups that are not covered either by opportunistic screening.

The aim of this study was therefore to evaluate the effect of socio-demographic factors and indicators for SES on the lower end of screening coverage in the BCSP and the higher end of the opportunistic screening coverage. Data of screening coverage in Flanders, Belgium were analyzed with a quantile regression model.[8]

Methods

Screening in Flanders

Flanders, the largest and most populated region in Belgium (around 6 million inhabitants), is among the regions with the highest BC incidence in Europe, despite the early implementation of a BCSP in 2001, offered biannually to women between 50-69 years.[1, 9] Women in Flanders can also choose to be screened for BC in opportunistic screening outside the BCSP. Where the BCSP is fully reimbursed by health insurance, opportunistic screening is not and does not have a systematic quality control such as daily quality checks of mammography equipment, double reading and case-based feedback to readers.[10] Although these two screening strategies coexist in Flanders, the combined coverage rate is only 64.1%, with 50.0% BCSP and 14.1% opportunistic screening.[11]

Data source

For this analysis, publicly available data for 2017 from the Center for Cancer Detection and regional authorities in Flanders were linked at a statistical sector level. The statistical sector level is the smallest level at which administrative information is systematically collected in Flanders and is comparable to the neighborhood in literature.[12] We will therefore use the term neighborhood hereafter. From the Center for Cancer Detection data were received of the screening invitations by the BCSP and attendances at the BCSP, as well as the attendances to the opportunistic screening. These data were collected in a collaboration between the Belgian Cancer Registry and the Center for Cancer Detection, as described by their respective statutes[13, 14] From the regional authorities data on socio-demographic characteristics were retrieved.[15] Linkage was performed in a protected environment and provided at an aggregated neighborhood level to mask all the individual level information. To prevent identification of any individual, neighborhoods were excluded that had less than five women screened. Due to that, 8690 of the 9490 neighborhoods in Flanders that provided the data of screening coverage rate in the BCSP and the opportunistic screening were included in this study. For these reasons, ethical approval was not needed for this study because the above-noted measures were taken for privacy protection.

Study variables

The primary outcome in this analysis was the coverage rate of screening in the BCSP, which was defined as the percentage of women aged 50-69 screened in the BCSP. The secondary outcome in this analysis was the coverage rate of opportunistic screening which was defined as the percentage of women aged 50-69 screened in the opportunistic screening.

The socio-demographic variables per neighborhood that were used as covariates are listed in table 1 and were defined as follows: 1) *Population density:* the number of residents per

km²; 2) *Same address as last year:* the percentage of residents with the same address as last year; 3) *Single parents:* the percentage of unmarried residents that are single and live together with at least one child; 4) *Married resident with child(ren) living at home*: the percentage of married residents that live together with at least one child; 5) *Unmarried cohabiting resident with child(ren) living at home:* the percentage of unmarried residents that live together with at least one child; 6) *The percentage of foreign residents:* the percentage of residents without Belgian nationality; 7) *Average personal annual income:* the quotient of the total net taxable income and number of residents on January 1 of the tax year; 8) *Average household size:* the average number of persons in a household.

Statistical analysis

Women were categorized into two groups, the group that was screened in the BCSP and the group that was screened in the opportunistic screening. In the first step of the analysis, the included neighborhoods in the analysis were ranked based on the coverage rates in the BCSP and in the opportunistic screening, respectively, and categorized in 9 quantiles (Q10-Q90). Then the socio-demographic variables were described per quantile. As we have aggregated data, these descriptions reflect the median estimates per quantile.

For each socio-demographic variable, to evaluate the deviations per quantile from the median regression for the central tendency of the data, multivariable quantile regression models were performed.. The regression coefficient per quantile was tested against 0 to determine the statistically significance of the coefficient. In addition, the slope of quantile regression lines per quantile was compared with the median regression slope with a Wald test to determine the significance of the difference. When the slope of quantile regression lines were significantly different from the slope of the median regression lines, the association between the determinants and screening coverage was indeed heterogeneous and the quantile regression was meaningful.[8, 16] All statistical tests were two-sided and considered statistically significant at 0.05. All analyses were performed in R 4.0.2.

Results

Description of the coverage and neighborhoods

Of the 8690 included neighborhoods in the analysis, the median coverage in the BCSP was 50%. The coverage in the 10th quantile (Q10) was 33.5% and in the 90th quantile (Q90), it was 64.5%. The median percentage of single-parents, the median percentage of foreign residents, and median average personal annual income decreased with increasing quantiles of BCSP coverage: for Q10 to Q90 of the BCSP coverage, the median per quantile decreased from 3.8% to 3.0%, 11.1% to 3.9%, and €21,100 to €19,500, respectively (Table 1).

The median coverage of the opportunistic screening was 12%, and for the Q10 to Q90 this increased from 4.2% to 24.8%. The median average personal annual income increased with the increasing quantiles of the coverage of the opportunistic screening from €18,700 to €21,700 for the Q10 to Q90 of the coverage of the opportunistic screening. (Table 2).

Determinants of the coverage in the BCSP

A significant difference between the coefficients of the quantile regression and the median regression was observed for population density, the percentage of foreign residents, the average household size, and the average personal annual income (Figure 1). These four determinants were all negatively associated with the coverage in the BCSP with median regression coefficients of -0.97, (95%CI: -1.09, -0.85), -0.20, (95%CI: -0.27, -0.13), -10.38, (95%CI: -12.84, -7.92), and -0.86, (95%CI: -0.97, -0.76), respectively (Table 3). At Q10, the statistically significant association of quantile regression of the percentage of foreign residents, average household size, and average personal annual income were stronger than the median regression, and the difference was statistically significant (Table 3). Of these three determinants, the regression coefficients and 95%CI for the Q10 of the coverage was -0.75, (95%CI: -0.85, -0.65), -13.59, (95%CI: -15.81, -11.37), and -1.05, (95%CI: -1.18, -0.92), respectively.

Determinants of coverage of the opportunistic screening

The coefficients of the quantile regression for most of the determinants were significantly different from the median regression (Figure 2). The percentages of single parent, average household size, and average personal annual income were positively associated with the coverage of the opportunistic screening. For these three variables, the coefficients and 95%CI of the quantile regression for the Q90 were 1.61, (95%CI: 1.28, 1.94), 17.15, (95%CI: 14.66, 19.63), and 1.72, (95%CI: 1.59, 1.85), respectively, which was significantly larger than the median regression coefficients 0.83, (95%CI: 0.64, 1.03), 7.86, (95%CI: 6.34, 9.38), and 1.10, (95%CI: 1.02, 1.17), respectively (Table 4).

Table 1 Description of the neighborhood-level socio-demographic variables and the coverage in the BCSP at the 10th (Q10) to the 90th (Q90) quantiles.*

Variables	Q10	Q20	Q30	Q40	Q50	Q60	Q70	Q80	Q90
Outcome									
Coverage in the BCSP [%]	33.5	40.0	43.8	47.2	50.0	53.2	56.2	59.9	64.5
Determinants									
Population density [1000 residents per km²]	1.1	1.4	1.4	1.4	1.1	1.3	1.1	1.1	0.9
Same address as last year [%]	91.7	91.9	92.3	92.5	93.1	93.1	93.6	93.6	94.3
Single parent [%]	3.8	3.5	3.4	3.3	3.3	3.2	3.1	3.1	3.0
Married resident with child(ren) living at home [%]	20.5	19.7	19.7	20.2	20.7	20.4	20.9	21.3	21.9
Unmarried cohabiting resident with child(ren) living at home [%]	6.4	6.2	6.4	6.2	6.3	6.2	6.3	6.1	6.1
The percentage of foreign residents [%]	11.1	6.2	4.8	4.4	3.9	3.7	3.7	3.4	3.9
Average household size [number]	2.5	2.4	2.4	2.4	2.4	2.4	2.4	2.5	2.5
Average personal annual income [1000€]	21.1	20.1	20.0	20.1	19.9	19.9	19.8	19.9	19.5

** The neighborhoods were ranked based on the coverage in the BCSP. The numbers in the table reflect the median value of the determinants per quantile of the coverage in the BCSP.*

Table 2 Description of the neighborhood-level socio-demographic variables and coverage of the opportunistic screening at the 10th (Q10) to the 90th (Q90) quantiles.*

Variables	Q10	Q20	Q30	Q40	Q50	Q60	Q70	Q80	Q90
Outcome									
Coverage of the opportunistic screening [%]	4.2	6.6	8.3	10.1	12.0	13.9	16.5	19.4	24.8
Determinants									
Population density [1000 residents per km²]	0.8	1.2	1.1	1.3	1.3	1.3	1.2	1.2	1.1
Same address as last year [%]	94.1	93.5	93.1	93.3	93.2	92.9	93.0	92.8	93.2
Single parent [%]	3.1	3.2	3.2	3.3	3.2	3.3	3.3	3.3	3.2
Married resident with child(ren) living at home [%]	21.6	20.7	21.2	20.6	20.7	20.4	20.3	20.3	21.1
Unmarried cohabiting resident with child(ren) living at home [%]	5.8	5.9	5.9	6.0	6.1	6.3	6.4	6.4	6.4
The percentage of foreign residents [%]	4.2	4.5	4.4	3.8	4.4	4.2	3.7	4.2	4.4
Average household size [number]	2.5	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.5
Average personal annual income [1000€]	18.7	18.8	19.1	19.3	19.7	19.8	20.5	20.6	21.7

** The neighborhoods were ranked based on the coverage of the opportunistic screening. The numbers in the table reflect the median value of the determinants per quantile of the coverage of the opportunistic screening.*

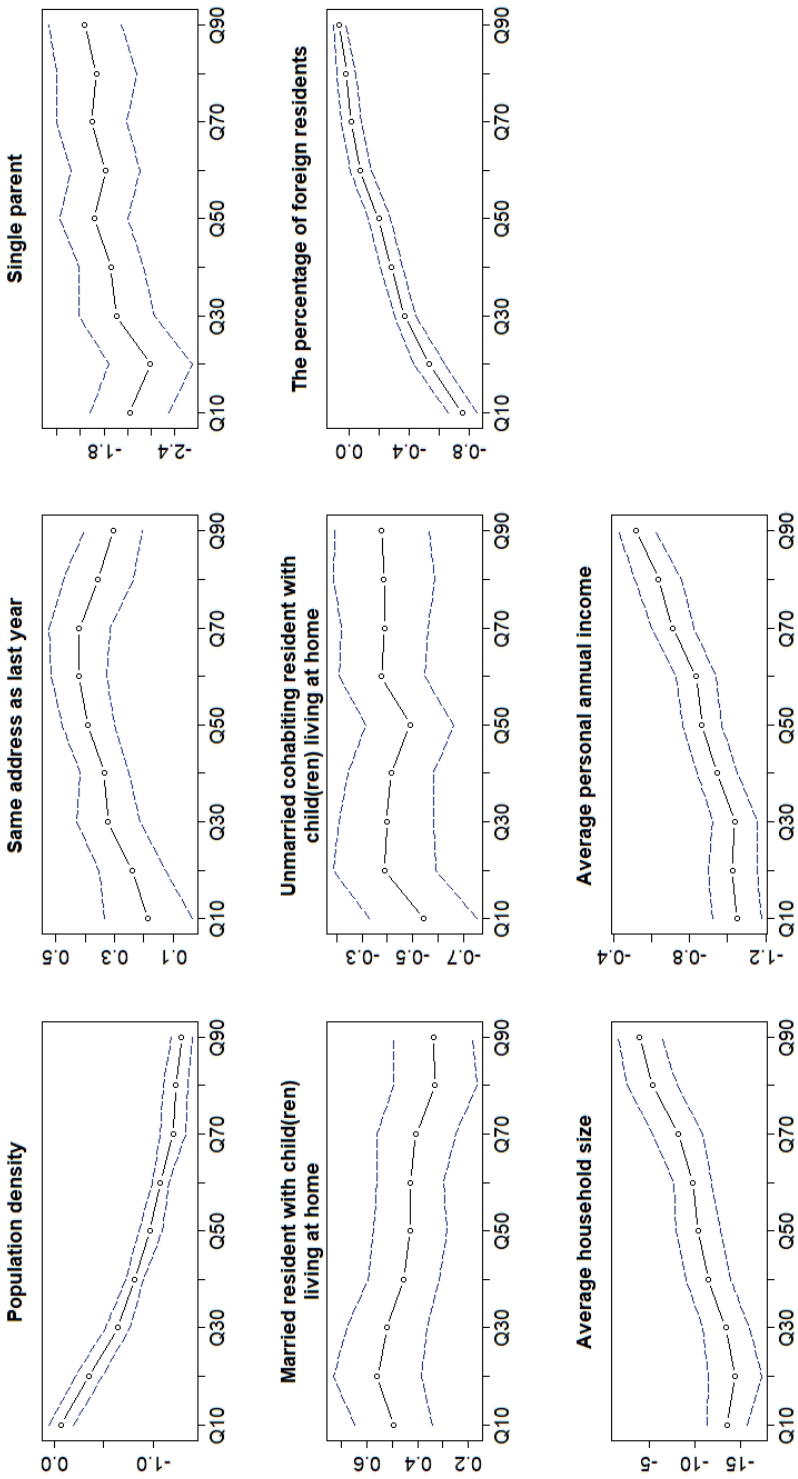

Figure 1 coefficients of the multivariable quantile regression of all the covariates as a function of the different quantiles of the coverage in the BCSP. The dotted line and the blue dash lines are the coefficient and the 95%CI of quantile regression at the different quantiles of the outcome.

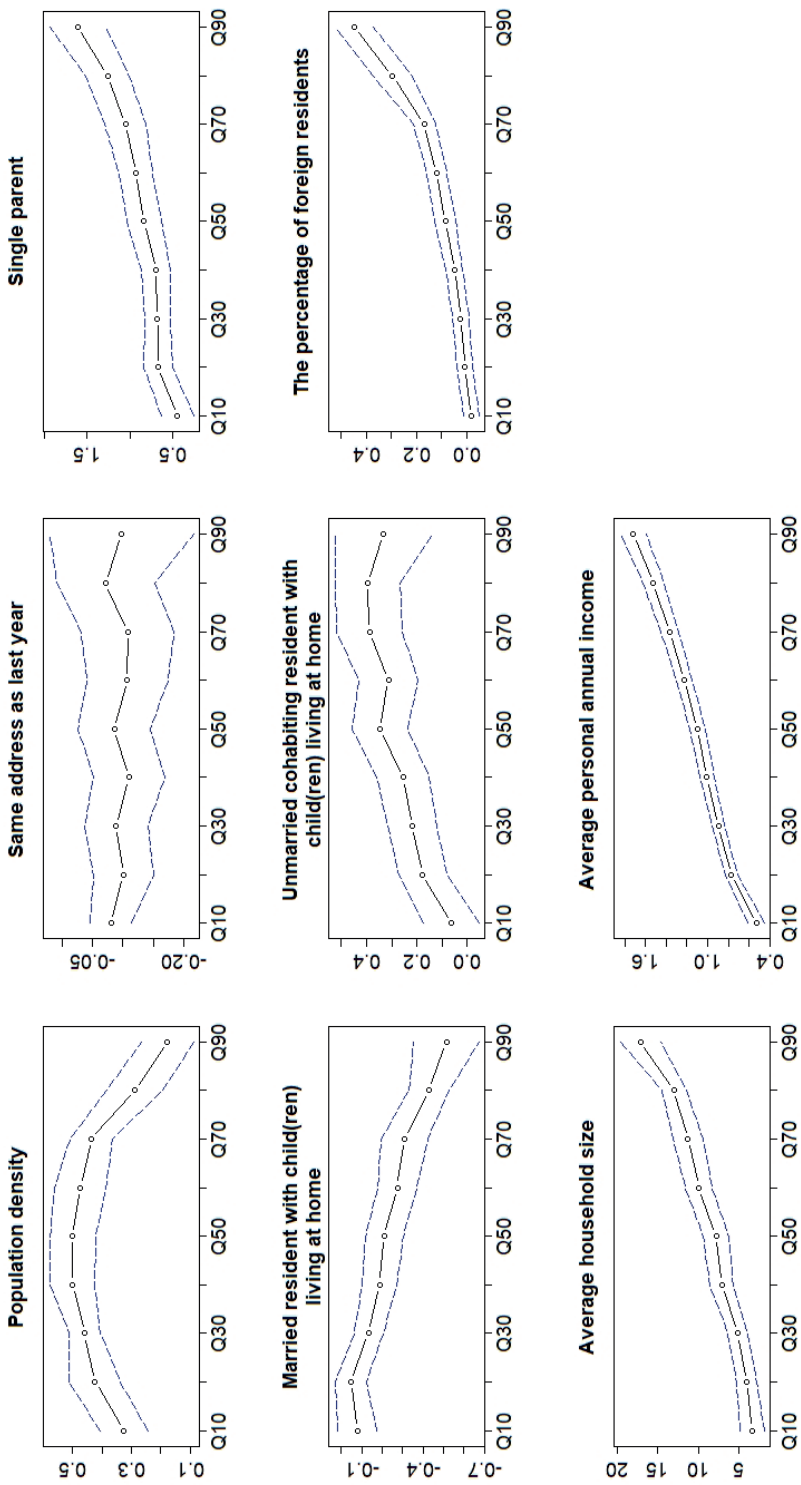

Figure 2 coefficients of the multivariable quantile regression of all the covariates as a function of the different quantiles of the coverage of the opportunistic screening. The dotted line and the blue dash lines are the coefficient and the 95%CI of quantile regression at the different quantiles of the outcome.

Table 3 multivariable quantile regression coefficient and 95%CI of the determinants of coverage in the BCSP at the 10th (Q10) to the 90th (Q90) quantiles.

Variables	Q10	Q20	Q30	Q40	Q50	Q60	Q70	Q80	Q90
Population density (1000 residents per km²)	-0.07	**-0.35**	**-0.65**	**-0.81**	**-0.97**	**-1.07**	**-1.20**	**-1.23**	**-1.29**
	(-0.19, 0.06)	(-0.49, -0.21)	(-0.77, -0.52)	(-0.90, -0.72)	(-1.09, -0.85)	(-1.16, -0.99)	(-1.32, -1.07)	(-1.35, -1.11)	(-1.39, -1.18)
	77.02***	38.95***	20.18***	7.80**		3.67	19.09***	23.68***	14.72***
Same address as last year (%)	0.19	0.24	**0.32**	**0.34**	**0.39**	**0.42**	**0.42**	**0.36**	**0.30**
	(0.04, 0.34)	(0.13, 0.35)	(0.21, 0.43)	(0.25, 0.42)	(0.30, 0.48)	(0.32, 0.52)	(0.32, 0.53)	(0.23, 0.48)	(0.21, 0.40)
	5.82*	4.32*	1.48	0.85		0.83	0.22	0.29	0.99
Single parent (%)	-2.02	-2.19	**-1.91**	**-1.86**	**-1.72**	**-1.81**	**-1.70**	**-1.74**	**-1.64**
	(-2.36, -1.68)	(-2.55, -1.84)	(-2.23, -1.58)	(-2.13, -1.58)	(-0.21, -1.42)	(-2.11, -1.52)	(-1.99, -1.40)	(-2.08, -1.40)	(-1.95, -1.33)
	1.38	5.77*	1.77	1.24		0.97	0.01	0.01	0.19
Married resident with child(ren) living at home (%)	0.49	0.56	**0.52**	**0.45**	**0.43**	**0.43**	**0.41**	**0.33**	**0.34**
	(0.34, 0.65)	(0.38, 0.73)	(0.36, 0.68)	(0.31, 0.59)	(0.29, 0.57)	(0.30, 0.56)	(0.25, 0.56)	(0.17, 0.50)	(0.18, 0.49)
	0.41	1.54	1.67	0.19		0.00	0.14	1.13	0.93
Unmarried cohabiting resident with child(ren) living at home (%)	-0.54	-0.39	**-0.40**	**-0.41**	**-0.49**	**-0.38**	**-0.39**	**-0.39**	**-0.38**
	(-0.75, -0.33)	(-0.59, -0.19)	(-0.58, -0.21)	(-0.58, -0.25)	(-0.66, -0.32)	(-0.55, -0.21)	(-0.56, -0.22)	(-0.59, -0.19)	(-0.57, -0.19)
	0.23	1.28	1.85	1.16		3.79	1.36	0.86	0.78
The percentage of foreign residents (%)	-0.75	-0.53	**-0.37**	**-0.28**	**-0.2**	**-0.08**	-0.02	0.01	**0.06**
	(-0.85, -0.65)	(-0.64, -0.43)	(-0.44, -0.30)	(-0.35, -0.21)	(-0.27, -0.13)	(-0.15, -0.01)	(-0.08, 0.05)	(-0.05, 0.08)	(0.02, 0.10)
	76.47***	28.66***	44.30***	8.66**		31.97***	41.31***	39.35***	50.62***
Average household size (number)	-13.59	-14.41	**-13.39**	**-11.51**	**-10.38**	**-9.78**	**-8.20**	**-5.36**	**-4.01**
	(-15.81, -11.37)	(-17.31, -11.50)	(-15.95, -10.84)	(-13.95, -9.07)	(-12.84, -7.92)	(-11.87, -7.69)	(-10.92, -5.48)	(-8.09, -2.63)	(-6.41, -1.60)
	3.18*	6.68**	8.73**	2.33		0.34	3.38*	9.47**	12.53***
Average personal annual income (1000€)	-1.05	-1.02	-1.04	**-0.95**	**-0.86**	**-0.83**	**-0.71**	**-0.63**	**-0.52**
	(-1.18, -0.92)	(-1.15, -0.89)	(-1.15, -0.92)	(-1.05, -0.84)	(-0.97, -0.76)	(-0.94, -0.73)	(-0.82, -0.60)	(-0.76, -0.51)	(-0.62, -0.42)
	4.90*	4.46*	9.34**	5.02*		0.85	20.28***	18.82***	44.61***

Numbers in bold: The 10th (Q10) to the 90th (Q90) quantile regression coefficient that was significantly different from zero at the 5% significance level.
*The 95%CI in parentheses. F statistics below the parentheses. *P < 0.05, **P < 0.01, ***P < 0.001.*

Table 4 multivariable quantile regression coefficient and 95%CI of the determinants of coverage of the opportunistic screening at the 10th (Q10) to the 90th (Q90) quantiles.

Variables	Q10	Q20	Q30	Q40	Q50	Q60	Q70	Q80	Q90
Population density (1000 residents per km²)	0.33	0.42	0.46	0.50	0.05	0.47	0.44	0.29	0.18
	(0.24, 0.41)	(0.34, 0.51)	(0.41, 0.51)	(0.42, 0.58)	(0.42, 0.58)	(0.39, 0.56)	(0.36, 0.51)	(0.20, 0.38)	(0.09, 0.27)
	9.65**	2.48	1.07	0.00		1.09	3.71	6.18*	9.44**
Same address as last year (%)	-0.08	-0.10	-0.09	-0.11	-0.09	-0.11	-0.11	-0.07	-0.10
	(-0.11, -0.05)	(-0.15, -0.05)	(-0.14, -0.04)	(-0.17, -0.05)	(-0.15, -0.02)	(-0.17, -0.04)	(-0.18, -0.03)	(-0.15, 0.01)	(-0.22, 0.02)
	0.01	0.16	0.01	1.19		0.81	0.44	0.04	0.04
Single parent (%)	0.45	0.67	0.68	0.7	0.83	0.93	1.05	1.26	1.61
	(0.26, 0.64)	(0.50, 0.84)	(0.52, 0.83)	(0.52, 0.87)	(0.64, 1.03)	(0.73, 1.12)	(0.81, 1.30)	(1.01, 1.51)	(1.28, 1.94)
	6.56*	1.93	3.88*	4.01*		1.61	2.81	8.66**	17.84***
Married resident with child(ren) living at home (%)	-0.08	-0.05	-0.13	-0.19	-0.21	-0.27	-0.31	-0.43	-0.51
	(-0.17, 0.02)	(-0.12, 0.03)	(-0.20, -0.06)	(-0.27, -0.10)	(-0.30, -0.12)	(-0.37, -0.18)	(-0.42, -0.91)	(-0.53, -0.33)	(-0.67, -0.36)
	5.32*	12.45***	5.81*	0.40		6.25*	8.20**	15.34***	19.06***
Unmarried cohabiting resident with child(ren) living at home (%)	0.06	0.18	0.22	0.26	0.35	0.31	0.39	0.40	0.33
	(-0.05, 0.17)	(0.08, 0.27)	(0.12, 0.32)	(0.15, 0.36)	(0.24, 0.46)	(0.20, 0.43)	(0.26, 0.52)	(0.27, 0.52)	(0.14, 0.53)
	19.61***	13.68***	6.40*	4.60*		1.02	0.67	0.30	0.02
The percentage of foreign residents (%)	-0.02	0.01	0.02	0.05	0.08	0.12	0.17	0.30	0.45
	(-0.05, 0.01)	(-0.02, 0.04)	(-0.01, 0.06)	(0.02, 0.08)	(0.04, 0.13)	(0.08, 0.16)	(0.12, 0.21)	(0.22, 0.37)	(0.37, 0.52)
	20.10***	11.57***	12.26***	10.31**		11.67***	18.69***	28.05***	146.57***
Average household size (number)	3.45	4.05	5.23	7.17	7.86	9.96	11.30	13.05	17.15
	(1.95, 4.94)	(2.82, 5.27)	(3.97, 6.49)	(5.71, 8.63)	(6.34, 9.38)	(8.32, 11.60)	(9.41, 13.19)	(11.52, 14.57)	(14.66, 19.63)
	37.66***	42.37***	21.00***	1.43		16.69***	26.22***	34.50***	83.72***
Average personal annual income (1000€)	0.53	0.77	0.90	1.01	1.10	1.23	1.36	1.53	1.72
	(0.45, 0.61)	(0.70, 0.83)	(0.84, 0.96)	(0.94, 1.08)	(1.02, 1.17)	(1.15, 1.30)	(1.28, 1.45)	(1.42, 1.63)	(1.59, 1.85)
	227.80***	71.65***	40.08***	11.31***		26.09***	47.88***	63.88***	49.11***

Numbers in bold: The 10th (Q10) to the 90th (Q90) quantile regression coefficient that was significantly different from zero at the 5% significance level.
*The 95%CI in parentheses. F statistics below the parentheses. *P < 0.05, **P < 0.01, ***P < 0.001.*

Discussion

We found that a larger percentage of foreign residents, a larger average household size, being indicators for lower SES were found in neighborhoods with a lower coverage in the BCSP. However, a higher average personal annual income, being an indicator for higher SES was also found in neighborhoods with a lower coverage in the BCSP. For these neighborhoods, the negative association between SES and coverage in the BCSP was stronger than in the neighborhoods that have relatively middle SES level. The neighborhoods with the higher coverage of opportunistic screening had a relatively higher average personal annual income and the positive association between the SES and coverage of the opportunistic screening was stronger in these neighborhoods than in the neighborhoods that have relatively lower SES level.

The median coverage in the BCSP was 50%, being 33.5% in the neighborhoods in the lowest quantile and 64.5% in the neighborhoods in the highest quantile. The coverage in the BCSP in Flanders was lower than in the countries like the Netherlands and the United Kingdom where BC screening is mainly performed in the BCSP, but it was close to countries like France and Germany where both the BCSP and opportunistic screening are performed for BC screening.[17] As the median coverage by the opportunistic screening was 12%, being 4.2% in the neighborhoods in the lowest quantile and 24.8% in the neighborhoods in the highest quantile, the combined coverage by the BCSP and the opportunistic screening was relatively close to the BC screening coverage in other Western European countries.[3, 17]

We observed that women in neighborhoods with a lower SES, as indicated by a crowded housing condition[18,19] or being an immigrant with a foreign nationality[20], tended to participate less in the BCSP than women in neighborhoods with middle level SES. The negative association between these variables and the coverage in the BCSP was also found previously in other European countries.[21, 22] Explanations for this phenomenon are that women with a relatively low SES have a lack of health literacy, leaving them less informed on the benefit of BCSP.[23] Other reasons may include the language barriers for women with an immigration background[24], and the fact that the hardship of life for women with relatively low SES may require more time to work than the high SES women and reduce the attention to health care.[25]

Interestingly, we also found that women in neighborhoods with a higher income as indicated by a higher average personal annual income also tend to participate less in the BCSP than the women in neighborhoods with middle level income. However, these women tend to participate more in the opportunistic screening than the women in neighborhoods with middle level income. Studies in France where screening in the BCSP and the

opportunistic screening coexist as the situation in Flanders also found that women in the most affluent group tend to participate more in the opportunistic screening.[26] The possible explanation for this phenomenon is that women who belong to the neighborhoods with a relatively high SES may prefer the opportunistic screening which has a more flexible time schedule and more personalized service than the BCSP.[2, 27]

Strength and limitation

The strength of this study is that the validity of the screening coverage data was warranted by the administrative database of the screening program in Flanders. The recall bias in the self-reported survey can be avoided in our data.[28] Moreover, the determinants of screening coverage were evaluated for the full distribution of the coverage in the BCSP and the opportunistic screening. The heterogeneous effect of the determinants of screening coverage in different quantiles can provide a more specific target for the potential interventions to improve the screening coverage rate. A limitation of this study is that all data were aggregated at the neighborhood level. It was not possible to explore the variation within the neighborhood due to the aggregated data. However, studies have shown that residents who live in the same neighborhood share similar SES and health behavior.[29, 30] and the association between the determinants in our study and the screening coverage was consistent with the literature. Another potential limitation of this study is the exclusion of neighborhoods that have less than five screened women, which is mainly related to the small size of a neighborhood. This measure is taken by the breast cancer screening program administrators with the aim to protect the privacy and is mandatory by the Flemish government. However, we think that the effect is this exclusion is limited due to the fact that we included 92% of all the neighborhoods.[31]

Conclusion

Women in the neighborhoods that had a relatively low SES, that are characterized by being an immigrant with a foreign nationality, and having a large average household size, as well as the women in the neighborhoods that had a relatively high SES, that are characterized by a high average personal annual income, participate less frequently in the BCSP. On the other hand, women who belong to the neighborhoods with a relatively high SES, tend to participate more in the opportunistic screening. Tailored intervention that aims to increase the equality of the coverage of the BCSP should pay more attention to women in these neighborhoods.

Additional Information

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PART 3

Quantification of overdiagnosis in breast cancer screening

CHAPTER 7

MAMMOGRAPHIC SENSITIVITY AS A FUNCTION OF TUMOUR SIZE: A NOVEL ESTIMATION BASED ON POPULATION-BASED SCREENING DATA

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Abstract

Background: Instead of a single value for mammographic sensitivity, a sensitivity function based on tumour size more realistically reflects mammography's detection capability. Because previous models may have overestimated size-specific sensitivity, we aimed to provide a novel approach to improve sensitivity estimation as a function of tumour size.

Methods: Using aggregated data on interval and screen-detected cancers, observed tumour sizes were back-calculated to the time of screening using an exponential tumour growth model and a follow-up time of 4 years. From the observed number of detected cancers and an estimation of the number of false-negative cancers, a model for the sensitivity as a function of tumour size was determined. A univariate sensitivity analysis was conducted by varying follow-up time and tumour volume doubling time (TVDT). A systematic review was conducted for external validation of the sensitivity model.

Results: Aggregated data of 22,915 screen-detected and 10,670 interval breast cancers from the Dutch screening program were used. The model showed that sensitivity increased from 0-85% for tumour sizes from 2-20 mm. When TVDT was set at the upper and lower limits of the confidence interval, sensitivity for a 20-mm tumour was 74% and 93%, respectively. The estimated sensitivity gave comparable estimates to those from two of three studies identified by our systematic review.

Conclusion: Derived from aggregated breast screening outcomes data, our model's estimation of sensitivity as a function of tumour size may provide a better representation of data observed in screening programs than other models.

Introduction

Breast cancer is the most common cancer and one of the main causes of death in European women, approximately one in seven women will develop breast cancer by the age of 75[1]. In recent decennia, mammography screening has been introduced in many countries. Studies have shown that screening can detect breast cancer at an earlier stage which will reduce treatment burden and improve survival.[2-4] However, there are ongoing debates on whether screening does more harm than good and on the related optimization of screening strategy. To inform these debates, it is important to evaluate breast cancer screening programs considering indicators of both long-term, such as decreasing burden of breast cancer-specific treatment and mortality benefit, and short-term indicators such as mammography sensitivity and specificity.[5,6] In this contribution, we focus on the estimation of mammographic sensitivity as a function of tumour size, which is highly relevant for the evaluation of screening programs.[7,8] However, we cannot measure sensitivity directly as there are no methods to determine the amount of asymptomatic cancers that are detectable by screening.[9]

Whereas most studies give one constant estimate for the sensitivity of mammography, Weedon-Fekjær et al. developed a logistic model to estimate the sensitivity of mammography as a function of tumour size.[10,11] In their studies, the sensitivity was estimated simultaneously with a continuous growth model utilizing breast cancer screening data, and back-calculation methods were used to estimate tumour size at screening from tumour size distributions of clinically detected tumours. Inspired by this approach, Swedish researchers estimated the sensitivity not only based on tumour size, but also breast density.[12,13] What is remarkable about the findings of their studies is that the sensitivity is 100% for tumours varying in size from 15-20 mm and over. However, this seems unlikely, as several studies showed that approximately 10-30% of all screen-detected tumours are larger than 20 mm, which indicated that at least a part of these tumours are missed at the size of 15-20 mm.[14-16] In addition, studies have shown that even tumours larger than 50mm can be invisible on mammography.[17,18]

In this study, we therefore aimed to provide a novel method to improve the estimates of mammography sensitivity as a function of tumour size by using aggregated data reported from a national population breast cancer screening program. We anticipate that the sensitivity function can be integrated into modelling studies focusing on the evaluation of breast cancer screening programs, which in turn can provide valuable evidence for the optimization of screening strategies.

Methods

A sensitivity model estimating mammographic sensitivity as a function of tumour size was developed in this study. To develop this sensitivity model, empiric data on number and sizes of screen-detected and interval cancers from a population-based breast screening program and back-calculation of these tumour sizes to the screening moment were used to determine the number of false negatives (FN). The model was externally validated on published data identified by a systematic review.

The sensitivity model: a description

In our sensitivity model, the probability of finding a tumour with volume V at screening moment i is based on the well-known formula for sensitivity:

$$S_i(V) = \frac{TP_i(V)}{TP_i(V) + FN_i(V)}$$

where $S_i(V)$ is the sensitivity to detect a tumour of volume V at screening round i, and $TP_i(V)$ and $FN_i(V)$ are the number of true-positives and false-negatives at screening round i as a function of tumour volume V respectively.

To determine the number of false-negatives as a function of volume we use the assumption that the undetected tumours at screening round i grow larger over time and will eventually be detected either at a subsequent screening round or as an interval cancer (Figure 1).

Let the number of screen-detected tumours at screening moment t_i be equal to N_i, where i =1,2, ... M runs over the total number M of screening moments in the screening program. Let the size of a tumour k which is screen-detected at screening moment t_i be equal to V_{ki}. Let the number of interval tumours between screening moment i and i+1 be equal to N'_i, where j =1...M-1 with corresponding tumour sizes V'_{kj}. Assume for each tumour k an exponential growth model where the volume at screening moment i is given by: $V_{ki} = V_k^0 * 2^{(t_i - t_0)/TVDT}$, where V_k^0 is the starting volume at time t_0 and $TVDT$ is the tumour volume doubling time. Now, from the tumour size detected by screening or intervals later than screening moment i, we can calculate back the tumour size at the time of screening using the exponential growth model.

If we assume an interval tumour is found at time t_j then the size of this tumour at screening moment t_i will be equal to: $V_{ki} = V'_{kj} * 2^{-(t_j - t_i)/TVDT}$. Also, the size of a tumour found in one

of the subsequent screening rounds $l > i$ can be calculated back in time to the size at the time of screening. If we assume a screen-detected tumour is found at time t_l then the size at screening moment t_i will be equal to: $V_{ki} = V_{kl} * 2^{-(t_l - t_i)/TVDT}$. Now, we can estimate the number of false negatives $FN_i(V)$ with volume V at screening moment i by

$$FN_i(V) = \sum_{j=i}^{M-1} N'_j\left(V'_{kj}\right) + \sum_{l=i+1}^{M} N_l(V_{kl})$$

i.e. the number of back-calculated interval tumours (N'_j) with size V at the time of screening plus the number of back-calculated subsequent screen-detected tumours (N_l) with size V at the time of screening t_i Together with the number of detected tumours at screening moment i given by $TP_i(V)=N_i(V)$, we can calculate the sensitivity $S_i(V)$ as a function of volume V.

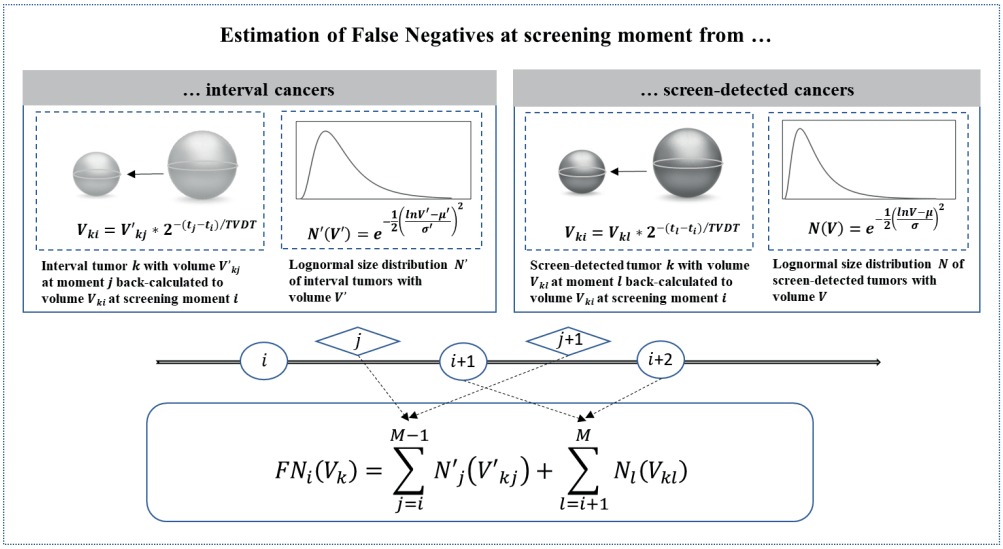

Figure 1 Estimation of false-negatives (FNs), where V_{ki} represents the volume of a tumour k at t_i, V'_{kj} and V_{kl} represent the volume of a tumour k during screening intervals ($j, j+1, \ldots$) and at subsequent screening rounds ($i+1, i+2,$) respectively, and the corresponding numbers of tumours are represented as N'_j and N_l. TVDT=Tumour volume doubling time.

The sensitivity model: input parameters

Tumour growth

For tumour growth, tumours were assumed to be spherical and to grow exponentially with a constant volume doubling time.[19] In this study, the tumour volume doubling time for women aged 50-70 years old was on average 157 days.[20] For the distribution of the screen-detected and interval tumour sizes, we used data from the Dutch breast cancer screening program from 2004 to 2009(Table 1).[14] The data from the first screening round was excluded as it is well known that in the first screening round relatively more and larger tumours are found compared to the subsequent screening rounds.[21] We used a nonlinear least-squares method to obtain the parameters of the log-normal tumour size distributions of the screen-detected and interval cancers found in the screening.

Table 1 Tumour size distribution of screen-detected cancers and interval cancers*

T categories (tumour size)	Distribution of screen-detected cancers	Distribution of interval cancers
T1a (≤5 mm)	7.7 %	2.2 %
T1b (>5 mm and ≤10 mm)	24.5 %	8.9 %
T1c (>10 mm and ≤20 mm)	49.0 %	40.0 %
T2 (>20 mm and ≤50 mm)	17.9 %	41.1 %
T3 (> 50 mm)	0.9 %	7.8 %

**Data source: National evaluation of breast cancer screening in the Netherlands, 1990- 2011/2012.*

Time since previous screening

We assumed biennial screening frequency as used in the Dutch screening program and many population-based breast screening programs. The maximum delay time in diagnosis after a false negative breast assessment in recalled women in a biennial screening program was 1251 days, which was rounded up to four years.[22] A median time from biennial screening to diagnosis of interval cancers of 502 days was used.[23] The time between the diagnosis of an interval cancer which had a possible false-negative result in the previous one or two screenings rounds was therefor set at 502 and 1232 (two years plus 502 days) days respectively. The time between the diagnosis of a screen-detected cancer which had a possible false-negative result in the previous one or two screening rounds was set at two years and four years, respectively.

Analysis of the results of the sensitivity model

The main outcome, i.e. tumour size-specific sensitivity estimated from the developed model was described graphically. To evaluate the uncertainty of our model, univariate sensitivity analyses were performed by varying input values of model parameters. Lastly, external validation of the developed model was conducted based on published data identified by a systematic review.

Analysis on the assumptions of the sensitivity model

We performed sensitivity analyses to evaluate the uncertainty of our model. The tumour volume doubling time was set to the lower and upper bounds of the 95% confidence interval (CI), which were 121 days and 204 days respectively[20], and the follow-up time between a screen-detected or interval cancer and the previous screening rounds was set at 2 and 6 years.

External validation of the sensitivity model

For external validation, we performed a systematic search in PubMed to find related articles focusing on mammography sensitivity and tumour size. The keywords used in the search included "breast carcinoma", "mammography", "sensitivity and specificity", and "tumour size". If the study reported observed sensitivities and related tumour size from a population-based screening program, then it would be included for further comparison. To ensure recent mammographic methods were used, the searches focused on relevant articles published from January 1, 2000 to August 1, 2020. Two authors searched the literature independently. A detailed description of the search strategies can be found in Supplementary data. From the included studies, the reported sensitivity was compared to our model.

Results

Mammography sensitivity according to the model

The aggregated data of 22,915 screen-detected cancers and 10,670 interval cancers were used for the estimation of tumour size distributions. For screen-detected cancers, the mean diameter and corresponding standard deviation (mm) were 14.0 (95%CI: 10.6-18.4) and 1.93 (95%CI: 1.52-2.46), while for interval cancers, these were 20.9 (95%CI: 18.5-23.8) and 1.77 (95%CI: 1.58-1.95), respectively. Given a TVDT of 157 days and a 4-year follow-up, the model showed a sensitivity function which continuously increased from 0 to 85% for tumour diameters between 2 and 20 mm (Figure 2: Solid line). The estimated sensitivity at 5, 10, 15 and 50 mm was 35%, 65%, 78%, and 97%, respectively.

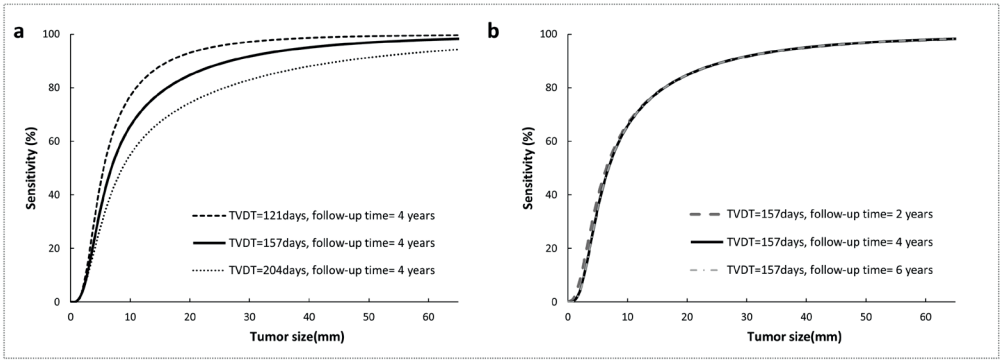

Figure 2 The estimated mammographic sensitivity as a function of tumour size. Solid line in a and b: the sensitivity model using a TVDT of 157 days and a follow-up time of 4 years; a: the sensitivity analysis of varying TVDT (121 and 204 days), and b: the sensitivity analysis of varying follow-up time (2, and 6 years). TVDT=tumour volume doubling time

Analysis on the assumptions

The mammography sensitivity increased with a decrease in TVDT (Figure 2). When the TVDT was set at the upper and lower limits of its confidence interval, the sensitivity for a 20-mm tumour became 74% and 93%, respectively. Unlike TVDT, different follow-up times only had a minor impact on our sensitivity model. Increasing the follow-up time to 6 years did not affect the sensitivity. With a shorter follow-up time (2 years), the sensitivity as found with our sensitivity model slightly increased when tumour size was smaller than 10mm. Specifically, the sensitivity was 39% and 67% for a 5 and a 10 mm tumour, respectively, whereas for larger tumour sizes, the sensitivity remained nearly unchanged.

External validation of the sensitivity model

After literature searching and screening, three studies were included [24-26]. All three studies reported mammography sensitivity and its related mean tumour size. To allow comparison, our estimated sensitivity at the mean tumour size reported in the literature (Table 2) was used. Specifically, our model gave reliable estimations which were comparable to two of the included studies [25,26]. However, the sensitivity was slightly underestimated compared to that of Cawson et al [24]

Table 2 Validation results based on screening data

Reference	Mean tumour size (mm)	Observed sensitivity (%)	Estimated sensitivity at the same size (%)
Cawson et al [24]	18.7	90.4 (84.7-94.6)	83.6
Moshina et al [25]	15.6	77.6 (75.6-79.6)	79.2
Skaane et al [26]	13.6	76.2(72.2-80.0)	75.7

Discussion

We developed a novel model for the estimation of mammographic sensitivity as a continuous function of tumour size, given that mammography's detection capability varies according to tumour size. Therefore, such a model provides more details about the sensitivity of mammography screening. Aggregated data of 22,915 screen-detected and 10,670 interval cancers from the Dutch screening program were used to obtain the size distribution of detected as well as missed breast cancers at the time of screening. The estimated sensitivity showed an increase from 0-85% for tumours between 2 and 20 mm. A sensitivity analysis for the model indicated that TVDT was an influential factor for sensitivity, and the assumption that a tumour will be detected in a biennial screening program within 2 screening rounds after one false-negative result was deemed appropriate.

In our model, the follow-up time was used to determine how long the expected time was that allows all false-negatives to be detected, so that sensitivity was not overestimated due to underestimations of false negatives. In this study, the follow-up time was estimated based on the maximum delay time in diagnosis (1251 days) reported in Ciatto et al., and we used a follow-up time of 4 years which was rounded up from the value 1251 days.[22] Although this study dates from 1992-2001, we estimated that this data on follow-up times is still valid in the current state of screening programs. First, according to a recently published study which compared the median delay time between two time periods of 1997-2006 and 2007-2016 in the Netherlands[27], the median delay time for both periods was approximately 2 years which was similar to the reported median delay time in Ciatto et al. Importantly, the difference in delay time between the two periods was not statistically significant. Second, delayed diagnosis after false negative results is not only related to mammography sensitivity itself, but also related to participants compliance as shown in Ciatto et al.[22] Third, the analysis on assumptions of our model showed that for a shorter follow-up time of 2 years, the screening sensitivity slightly increased, whereas for a longer follow-up time of 6 years, the sensitivity curve barely changed compared to that of 4 years. These results indicate that a follow-up time of 4 years is reasonable.

The validation of our model showed that the estimated sensitivity was comparable to two of the three studies[25,26], whereas the sensitivity was slightly underestimated compared to that of Cawson et al.[24] A possible reason is that in the study of Cawson et al., only tumours that could be detected or were visible on mammograms were included. However, it is well-known that in a real-world screening setting a proportion of tumours is not detectable by mammography[18], which could explain the higher sensitivity reported. Although the model was generated based on data from Dutch breast cancer screening program, we anticipated that this model could also be applicable globally to other organized population screening

programs with biennial mammography like Norway and Australia. This assumption was informed by several studies which suggest that screening interval plays a vital role in estimating mammography sensitivity.[28] Second, in addition to tumour size, mammography sensitivity can also be affected by participants' characteristics such as mammographic density, and technical factors such as interpretive skills of radiologists.[29] We expect that these factors might not differ much between the Netherlands and the other two countries, and therefore could be used as reliable sources for our external validation.

Compared to other models where a seemingly optimistic sensitivity of 100% for tumour diameters of 15-20 mm was estimated[10-13], our model provides a more reliable sensitivity of 85% for a tumour diameter of 20 mm. Studies have shown that on average 20% of the screen-detected cancers were larger than 20 mm, and data from Germany showed that approximately 8% of the incident tumours in their population screening program were even larger than 50 mm.[14-16] Although infrequent screening or fast-growing cancers could partly explain these larger tumour sizes, it is unlikely that the sensitivity would reach a perfect sensitivity at a size of 20 mm. In addition, several studies have shown that some cancers will not be visible on mammograms even at a very large size >70mm[18,30,31], as factors like sites where visualization is difficult (close to the thorax wall), and especially high-density breast tissue will lead to not-detectable tumours on mammograms.[18,32]

The shape of the sensitivity curve in our study was similar to models estimated from logistic functions (Figure 3).[10-13] However, our model showed a higher sensitivity for tumours ≤10mm, while the sensitivity became lower when the tumour size was larger than 10mm. Possible reasons could be mainly explored from the model structure perspective. First, in our model, we did not make a prior assumption on the sensitivity function itself such as a logistic function that was used in other studies. By assuming a logistic function, the sensitivity would increase sharply at a certain point as observed in Figure 3, which might lead to a higher sensitivity for larger tumours than that of our model. Second, certain aspects of the tumour growth model might be possible reasons. To be specific, in our model, we assumed that tumour grows through an exponential function with a constant TVDT, according to Collins et al.[19] However, in Weedon-Fekjær et al., they used a growth model made by Spratt et al., in which tumour was assumed to grow through a logistic function with variation in individual growth rates.[33,34] In studies from Isheden et al. and Abrahamsson et al., although they also used an exponential model, the cell reproductive rate with a constant inverse growth rate was used as their parameters. Tumour growth rate had a crucial impact on the estimation of sensitivity as a faster growing tumour was more likely to be detected at a larger volume than a slower growing tumour, which might result in a higher sensitivity.[35] Nevertheless, it is difficult to compare in a straightforward way as conflicting results were reported on which model performs well and as different parameters were used to express tumour growth in these studies.[36,37]

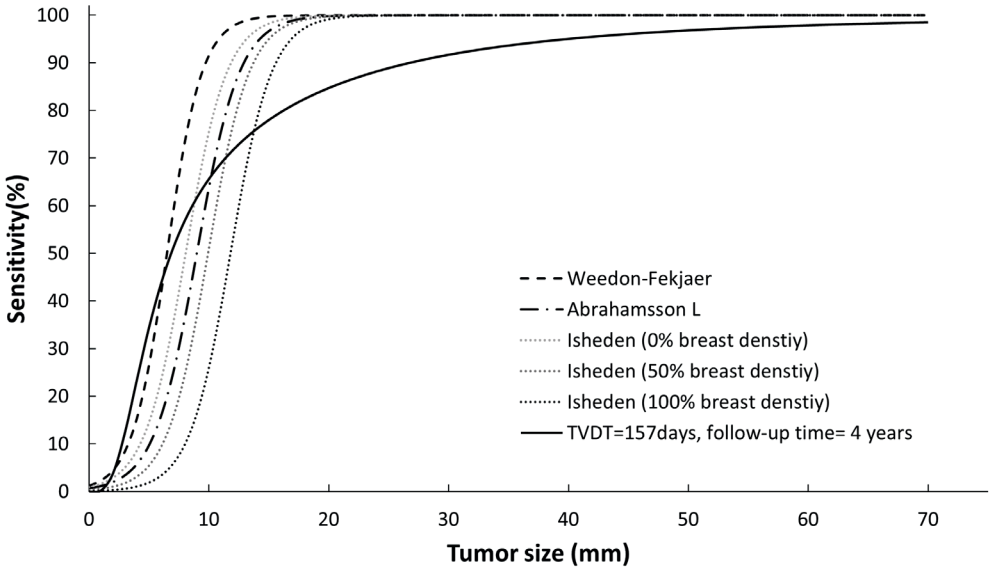

Figure 3 A comparison of the proposed sensitivity function model with other model studies. Data for 100%, 50%, and 0% breast density of Isheden et al.[12], of Weedon-Fakjaer et al.[10], and of Abrahamsson et al.[13]. TVDT= tumour volume doubling time.

In addition to models that estimate screening sensitivity continuously as a function of tumour size, the MISCAN model calibrated mammographic sensitivity by T-stage. The sensitivity of our model was generally lower than the estimations of sensitivity in studies that used the MISCAN model.[39,40] For example, the estimated sensitivity at ≤5, 5-10, 10-20 and >20mm was 47%, 62%, 90% and 98% in Gelder et al.[39], while the estimated sensitivity for a tumour at 5, 10, and 20 mm in our model was 35%, 65%, and 85%. One of the possible reasons could be the inclusion of prevalent cancers detected at the first screening round[40], which might lead to a higher sensitivity in the MISCAN model.

The strengths of this study lie in several aspects. Firstly, unlike other modeling studies that assumed a logistic function[10-13], we estimated a sensitivity model without any prior assumptions. Secondly, we used real-world aggregated data such as the number and size distribution of breast cancers, which can be relatively easily found in the national reports of breast cancer screening programs. Furthermore, the developed model can be easily adapted with different input parameters such as growth rates, different tumour size distributions and interval periods, which could make our sensitivity model useful for screening evaluation in other countries or other screening purposes.

However, there are also some limitations. Firstly, we used population-based data such as the number and size distribution of breast cancers based on T-stage, however, with a more detailed tumour size distribution instead of just the T-stage, the estimation of the lognormal distribution parameters would be more reliable. Secondly, the sensitivity model used a constant tumour diameter doubling time for every tumour, while in reality, the tumour growth varies widely among tumours or even for one tumour at different times.[19,41] Ideally, a comprehensive growth model could be incorporated if more detailed data were available. Thirdly, in our model, we assumed that all false-negative cancers would be detected in the future and became larger over time. However, studies have shown that some cancers will stop growing and even regress, which might lead to an overestimation of the sensitivity.[42] On the other hand, some fast-growing cancers would be recognized as false-negatives instead of new incident cancers, which might underestimate sensitivity.[43] Moreover, we assumed that the time between two screening rounds and the time between the last screening and an interval cancer was fixed. However, knowledge about these time distributions would enable us to better estimate the distribution of tumour sizes at time of screening. Lastly, in addition to tumour size, breast density and age also has an impact on mammographic sensitivity. Studies have shown that mammography sensitivity decreases in women with dense breasts and younger women.[44] The model presented here gives the sensitivity of mammography as used in screening settings for a population of women with mixed breast density and age. However, the sensitivity as a function of tumour size could in principle also be calculated for women with dense or fatty breasts or for different age groups if specific data on these groups of women were available.[12]

Conclusion

In this study, we developed a model which estimates the sensitivity of mammography as a function of tumour size without any prior assumptions about the function itself. The sensitivity model showed a similar sensitivity curve shape compared with studies that were estimated from logistic function [10-13], but the estimates in our model had a better representation of data observed in other screening programs. Furthermore, as tumour growth is an influential factor for the estimation of sensitivity, future studies that provide more detailed information on tumour progression, such as tumour doubling times, would help in further refining sensitivity estimates. In summary, our work provides knowledge on the tumour size-specific sensitivity of mammography. Our sensitivity model can be incorporated in cost-effectiveness models aiming to evaluate breast cancer screening programs. A tumour size-specific sensitivity might improve the performance of cost-effectiveness modeling compared with models that use only a single value for mammographic sensitivity.

Supplementary data

Search strategy

("Breast Neoplasms"[Mesh] OR breast cancer*[tiab] OR breast tumo*[tiab] OR breast carcinom*[tiab] OR mammary cancer*[tiab] OR cancer of breast[tiab] OR cancer of the breast[tiab] OR breast malign*[tiab] OR breast neoplasm*[tiab])
AND
("Mammography"[Mesh] OR mammogra*[tiab])
AND
("Sensitivity and Specificity"[Mesh] OR sensitiv*[tiab] OR false negative[tiab])
AND
(size[tiab] OR tumour siz*[tiab] OR tumour siz*[tiab] OR tumour diamet*[tiab] OR tumour diamet*[tiab] OR tumour volum*[tiab] OR tumour volum*[tiab])
AND
("Mass Screening"[MeSH] OR screen*[tiab])

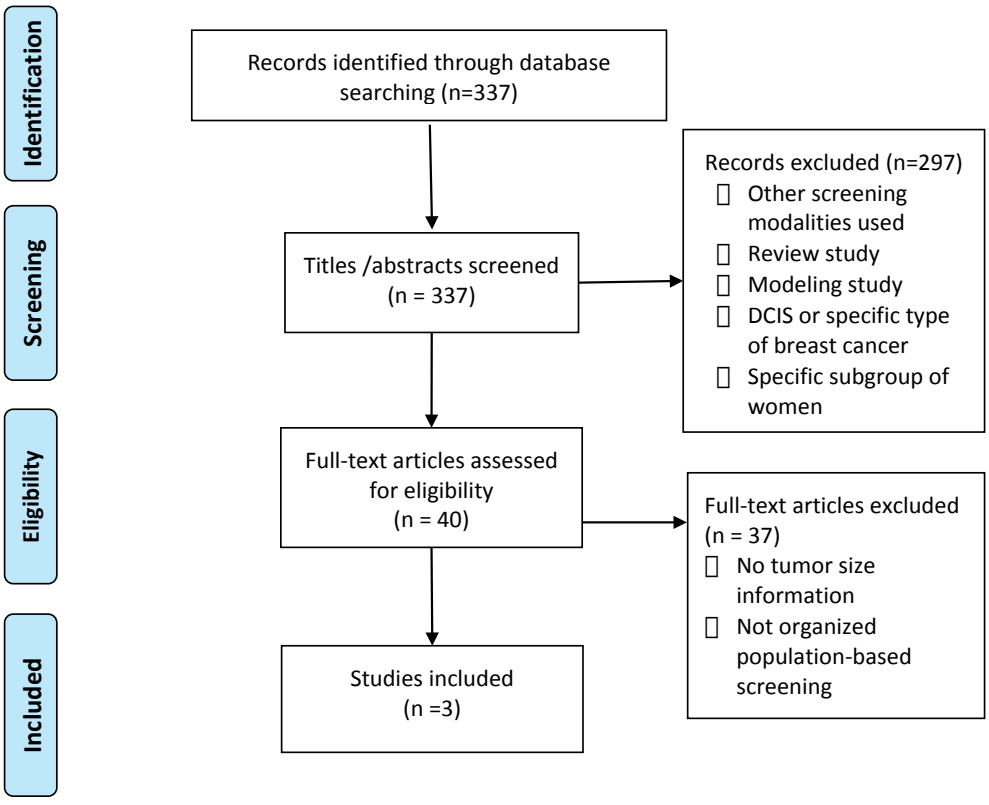

Figure S1 Flowchart of literature search

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CHAPTER 8

OVERDIAGNOSIS OF INVASIVE BREAST CANCER IN POPULATION-BASED BREAST CANCER SCREENING: A SHORT- AND LONG-TERM PERSECTIVE

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Abstract

Background Overdiagnosis of invasive breast cancer (BC) is a contentious issue.

Objective To estimate the overdiagnosis rate of invasive BC in an organized BC screening program, and to evaluate the impact of age and follow-up time.

Methods The micro-simulation model SiMRiSc was calibrated and validated for BC screening in Flanders, where women are screened biennially from age 50 to 69. Overdiagnosis rate was defined as the number of invasive BC that would not have been diagnosed in the absence of screening per 100,000 screened women during the screening period plus follow-up time (which was set at five years and varied from two to fifteen years). Overdiagnosis rate was calculated overall and stratified by age.

Results The overall overdiagnosis rate for women screened biennially from 50 to 69 was 20.1 (95%CI:16.9-23.2) per 100,000 women screened at five years follow-up from stopping screening. Overdiagnosis at five years follow-up time was 12.9 (95%CI:4.6-21.1) and 74.2 (95%CI:50.9-97.5) per 100,000 women screened for women who started screening at age 50 and 68, respectively. At two and fifteen years follow-up time, overdiagnosis rate was 98.5 (95%CI:75.8-121.3) and 13.4 (95%CI:4.9-21.9), respectively for women starting at age 50, and 297.0 (95%CI:264.5-329.4) and 34.2 (95%CI:17.5-50.8), respectively for those starting at age 68.

Conclusions Sufficient follow-up time (≥10 years) after screening stops is key to obtaining unbiased estimates of overdiagnosis. Overdiagnosis of invasive BC is a larger problem in older compared to younger women.

Keywords: Breast Neoplasms, Mammography, Mass screening, Overdiagnosis, Modeling studies, Invasive breast cancer

Introduction

Population-based mammographic screening has been implemented in most high-income countries to reduce breast cancer-specific mortality.[1] While population-based mammographic screening has the potential to achieve up to 40% breast cancer-specific mortality reduction, one of the most concerning harms in breast cancer screening is overdiagnosis.[1] Overdiagnosis of breast cancer refers to the detection of breast cancers that would not have been diagnosed in the absence of screening.[2]

Overdiagnosis has gained increasing attention in the past decade, along with the advocacy for informed decision-making based on both the benefit and harms of breast cancer screening.[3,4] Studies on overdiagnosis in general combine invasive breast cancer and ductal carcinoma in situ (DCIS).[5–7] Although there is agreement that screen-detected DCIS contributes to overdiagnosis[8], the estimation of overdiagnosis of invasive breast cancer remains a contentious issue. The published data on the proportion of overdiagnosed invasive breast cancers range from -0.2% to 54%.[2,9,10] Among the many explanations for this wide range of estimates are: the applied denominator of the proportion of overdiagnosedcaners[11], different tumour growth velocities[12], varying breast cancer background incidence,[13] and the follow-up time used in the analysis[11,14] When screening is initiated, short-term breast cancer incidence will rise since many cancers are found earlier than they would have been without screening.[12] Therefore, to properly estimate overdiagnosis, it is necessary to have a sufficiently long period of follow-up time to compensate for this lead time effect.[11,14] In general, overdiagnosis is reported as one estimate for a whole population.[5,6,9,15–20] This is also the case in studies where overdiagnosis was informed as one estimate to all individual women to help them make informed decisions.[3,4] However, overdiagnosis is likely to be different for women in different age groups given the different breast cancer incidence rate and tumour growth rate.[21,22]

Therefore, the aim of this study was to quantify the overdiagnosis of invasive breast cancer for women who were screened biennially from age 50 to 69 in the population-based breast cancer screening program in Flanders, and to quantify the influence of age and follow-up time on overdiagnosis rate. In this study, we focused on the estimation of overdiagnosis of invasive breast cancer in a screened population, overall, as well as for women at different ages.

Methods

Breast cancer screening in Flanders

In Flanders, a population-based breast cancer screening program has been implemented since 2001.[23] Every two years, women aged 50-69 with no history of breast cancer in the last ten years are invited to screen by mammography unless they actively opt-out.[24]

The SiMRiSc model: description, input, outcomes, and validation

The micro-simulation model SiMRiSc[25] was applied to the population-based breast cancer screening program in Flanders and has been previously described in detail.[25–28] A virtual cohort of women was created and followed from birth. Every woman was assigned an age of death based on data of the life expectancy of women in Flanders.[29,30] For each woman, the probability of developing invasive breast cancer and the age at clinical diagnosis was derived from the invasive breast cancer incidence rate of women in Flanders.[29] A normal distributed breast cancer incidence risk and a log normal distributed clinical (self-) detection risk was assumed characterized by the distribution (geometric) mean and standard deviation. The tumour growth parameters and the tumour size at clinical self-detection were determined from literature.[21,31] For each woman who had incident breast cancer, an age-dependent tumour volume doubling time was sampled from a log-normal distribution and applied in an exponential tumour growth model to determine the individual tumour growth history.[26] During the screening period, developing invasive breast cancers could be detected by mammography. The model used a screening sensitivity based on tumour size and breast density[32,33], where breast density was modeled as a function of age.[34–36] The risk of tumour induction due to ionizing radiation from mammography was also considered based on the relative risk model described in the BEIR7 report.[37] Tumours that became clinically evident by self-detection between screening rounds were assigned as interval cancers. The preclinical period of a tumour was defined as the time the tumour developed from a minimal screen-detectable tumour diameter of 5mm until it became clinically evident by self-detection.[21] Women with a screen-detected or self-detected invasive breast cancer were removed from the screening and assigned a breast cancer-specific death probability based on tumour diameter at diagnosis, which was based on the relative survival of breast cancer patients in the Belgian Cancer Registry (BCR).[29] All other women stayed in the screening until the end of the screening, or death.

All input parameters were derived from literature and data from the BCR and Statistics Belgium (Table S1), who also have access to reimbursed-based screening data. The incidence and relative survival rate of breast cancer for women of all ages from 2000 to 2017 were provided by the BCR. The all-cause mortality for women of all ages from 2000 to 2017 was provided by Statistics Belgium.

The model was validated by comparison of modelled outcomes to the empirical 95%CI of the observed data from the BCR and the Center for Cancer Screening (CvKO) in the first and second screening round. The outcomes used for comparison include the number of screen-detected and interval breast cancers and the size distribution of the screen-detected breast cancers in the first and second screening round from the year 2015. For model validation, the screening was simulated for women who started biennially screening between 50 and 69 years of age until age 69. The outcomes of the model were calculated for each birth cohort and subsequently calculated for the four age groups 50-54, 55-59, 60-64, and 65-69 years of age and standardized per 1000 screened women.

Quantification of overdiagnosis

Based on the above-noted formulation of the SiMRiSc model, a cohort was modeled from birth to death. To get an overall estimate of overdiagnosis, the simulation was performed for the biennial screening in a cohort for women who were screened biennially from age 50 to 69. As a control, the same cohort was created without screening and followed during lifetime for the incidence of breast cancer or death. In this control cohort, all observed cancers were clinically diagnosed.

Overdiagnosed cancers were defined as invasive cancers detected by screening that would not have presented clinically during the screening period and the follow-up time after screening stops. We calculated the number of overdiagnosed invasive breast cancers by comparing the number of diagnosed invasive cancers in a screened cohort to the number of diagnosed invasive cancers in a control cohort from the start of screening to the end of follow-up. The proportion of overdiagnosed cancers was defined as the number of overdiagnosed breast cancers divided by the number of screen-detected and interval cancers in the screened cohort, in which the interval cancers were defined as the breast cancers diagnosed between the current screening age and the next scheduled screening age in two years. Furthermore, as shown by many papers, the proportion of overdiagnosed cancers is strongly influenced by what is used as a denominator.[11,38] Therefore the absolute number of overdiagnosed cancers per 100,000 screened women was also calculated. The follow-up time was included because, in the screened cohort compared to the control cohort, more breast cancers will be diagnosed during screening and less breast cancers will be diagnosed after screening stops.

To evaluate the effect of age on overdiagnosis, simulation was also performed in single birth cohorts in which the screening start age varied by every two years from 50 to 69 and screened only once for each birth cohort. To evaluate the effect of prevalence mammography at age 50, the probability of overdiagnosis conditional to having had one, two, and three negative mammograms was also simulated.

For all simulations, the follow-up time was varied from two to fifteen years after the screening. For each cohort, a 100% screening uptake was applied, and ten iterations were performed. The mean and 95% confidence interval (CI) of the overdiagnosis rate were calculated from the ten iterations.

Sensitivity analysis

The robustness of the outcomes of the model was evaluated in a univariate sensitivity analysis, where the upper and lower limit of the 95%CI of the input parameters was applied. The impact of low participation was also tested in the sensitivity analysis. Screening participation of 50% was evaluated where the probability of being screened was 50% for a woman in the last 2 years. As the baseline estimate for the sensitivity analysis, the overdiagnosis rate for women screened once from age 50 with five years follow-up time was used. For simplicity, one iteration was performed in the sensitivity analysis. The sensitivity analysis results were summarized in a tornado plot.

Results

Validation of the model

The simulated number of screen-detected breast cancers corresponded well with the observed data, albeit with a slight overestimation in the younger age groups of 50-54 and 55-59 (Table 1). The simulated number of interval breast cancers in the second screening round was also slightly overestimated, whereas the simulated number of interval breast cancers in the first screening round corresponded well with the observed data. The simulated size distribution of the diagnosed breast cancers corresponded well with the observed values in the first and second screening round for all age-groups with a slight underestimation of large-sized cancers (>2cm) in the second screening round.

Table 1 Results of the model validation. Comparison between the simulated and observed data.

	Observed 95%CI* (Flanders data)	Simulated
Number of screen-detected tumors (per 1000 screenings)		
The first screening round		
50-54	4.7 (4.0-5.5)	4.4
55-59	7.3 (4.6-10.1)	5.6
60-64	9.8 (5.5-14.1)	6.2
65-69	12.1 (6.5-17.7)	7.8
The second screening round		
50-54	2.9 (2.3-3.5)	4.0
55-59	3.8 (3.3-4.3)	4.5
60-64	5.4 (4.7-6.0)	5.1
65-69	6.4 (5.7-7.1)	6.1
The tumor size distribution of screen-detected breast cancer		
First screening round		
<1cm	24.2% (17.3%-31.0%)	21.9%
1-2cm	43.6% (35.7%-51.6%)	46.9%
>2cm	32.2% (24.7%-39.7%)	31.3%
The second screening round		
<1cm	28.5% (25.1%-31.8%)	25.9%
1-2cm	48.9% (45.2%-52.6%)	55.9%
>2cm	22.7% (19.6%-25.8%)	18.5%
Number of interval cancers (per 1000 screenings)		
After the first screening round	3.5 (2.9-4.1)	3.1
After the second screening round	2.6 (2.3-2.8)	2.9

**Data source: The Belgian Cancer Registry. [29] Index year: 2015.*

Table 2 Mean and 95%CI of the number of screen-detected and interval cancer, the number of overdiagnosed breast cancer and the overdiagnosis rate of women who were screened biennially from age 50 to 69 with follow-up time after screening stops varied from 2 to 15 years.

Follow-up time after screening stops at age 69	Number of overdiagnosed breast cancers	Number of screen-detected breast cancers	Number of interval breast cancers	Number of mammograms performed	Overdiagnosis rate (per 100,000 women biennially screened)	Proportion of overdiagnosed cancers *
2 years	326 (291-361)	3,657 (3,556-3,758)	2,323 (2,213-2,433)	804,033 (802,351-805,715)	40.5 (36.0-45.0)	5.4% (4.8%-6.1%)
3 years	232 (202-261)				28.8 (24.9-32.7)	3.9% (3.3%-4.4%)
4 years	186 (161-210)				23.1 (19.9-26.3)	3.1% (2.7%-3.6%)
5 years	162 (137-186)				20.1 (16.9-23.2)	2.7% (2.2%-3.1%)
10 years	144 (129-158)				17.8 (16.0-19.7)	2.4% (2.1%-2.7%)
15 years	143 (123-163)				17.8 (15.2-20.4)	2.4% (2.0%-2.8%)

** Denominator of the proportion: the number of screen-detected plus the number of interval breast cancer*

Table 3 Estimates of the mean and 95%CI of the number of overdiagnosed breast cancers per 100,000 women screened once at different follow-up times after screening stops for women with different screening start age.

Screen start age	2 years	3 years	4 years	5 years	10 years	15 years
50	98.5 (75.8-121.3)	44.6 (34.1-55.1)	21.6 (10.8-32.4)	12.9 (4.6-21.1)	12.3 (5.3-23.0)	13.4 (4.9-21.9)
52	107.9 (94.1-121.6)	47.6 (36.3-59.0)	20.3 (12.5-28.1)	12.1 (6.5-17.8)	12.1 (5.3-19.0)	12.4 (5.5-19.2)
54	121.1 (104.4-137.8)	53.6 (39.8-67.3)	24.9 (16.5-33.5)	15.5 (7.4-23.7)	12.3 (7.5-17.1)	13.4 (6.6-20.3)
56	138.2 (113.4-162.9)	60.8 (49.1-72.5)	28.4 (16.3-40.5)	16.8 (5.2-28.3)	13.2 (5.5-20.9)	16.4 (3.2-29.6)
58	139.0 (112.8-165.1)	58.8 (42.2-75.3)	27.6 (15.2-39.9)	16.1 (6.6-25.6)	12.3 (5.3-19.4)	14.0 (6.1-22.0s)
60	148.8 (131.3-166.4)	70.1 (54.1-86.1)	37.4 (23.3-51.6)	24.2 (13.1-35.2)	17.1 (9.3-25.0)	16.6 (9.8-23.5)
62	167.6 (144.0-191.3)	82.3 (64.2-100.5)	47.4 (34.8-59.9)	32.9 (18.8-47.0)	21.8 (12.4-31.2)	22.5 (14.5-30.5)
64	186.3 (157.0-215.7)	95.4 (73.0-117.8)	62.9 (48.4-77.3)	51.0 (36.4-65.6)	22.8 (9.1-36.4)	21.8 (11.8-31.8)
66	239.1 (196.0-282.2)	155.9 (126.2-185.6)	119.2 (98.7-139.8)	76.0 (56.2-95.9)	31.9 (16.8-47.0)	29.0 (19.1-38.9)
68	297.0 (264.5-329.4)	176.7 (144.0-209.3)	110.2 (80.9-139.6)	74.2 (50.9-97.5)	36.7 (20.6-52.9)	34.2 (17.5-50.8)

Table 4 Overdiagnosis conditional on having had one, two, and three negative mammograms. Numbers are per 100,000 women biennially screened with follow-up time after screening stops varied from 2 to 15 years.

Follow-up time after screening stops	Overdiagnosed breast cancers per 100,000 women biennially screened conditional to number of prior negative screens			
	age 50	age 52 after 1 negative mammogram	age 54 after 2 negative mammograms	age 56 after 3 negative mammograms
2 years	98.5 (75.8-121.3)	50.9 (40.9-61.0)	37.2 (31.3-43.0)	30.6 (23.4-37.8)
3 years	44.6 (34.1-55.1)	23.6 (17.7-29.4)	18.4 (14.5-22.3)	15.8 (12.4-19.2)
4 years	21.6 (10.8-32.4)	10.9 (7.1-14.6)	9.0 (6.8-11.1)	8.8 (5.1-12.7)
5 years	12.9 (4.6-21.1)	10.7 (6.1-15.3)	11.5 (8.4-14.5)	10.2 (5.9-14.5)
10 years	12.3 (5.3-23.0)	7.8 (4.1-11.6)	8.8 (5.3-12.2)	9.1 (6.4-11.8)
15 years	13.4 (4.9-21.9)	7.6 (4.2-10.9)	7.4 (3.5-11.3)	7.9 (3.5-12.4)

Estimation of overdiagnosis

The overall overdiagnosis rate of invasive breast cancer for women screened biennially from 50 to 69 was 20.1 (95%CI:16.9-23.2) per 100,000 women screened at five years of follow-up time, whereas overdiagnosis was 40.5 (95%CI:36.0-45.0) and 17.8 (95%CI:15.2-20.4) per 100,000 women screened for two and fifteen years follow-up time, respectively (Table 2). The overall proportion of overdiagnosed cancers decreased from 5.4% (95%CI:4.8%-6.1%) to 2.4% (95%CI:2.0%-2.8%) for two and fifteen years follow-up time, respectively (Table 2).

Overdiagnosis rate at five years follow-up time was 12.9 (95%CI:4.6-21.1) and 74.2 (95%CI:50.9-97.5) per 100,000 women screened for women who started screening at age 50 and 68, respectively (Table 3).

For women screened at age 50, overdiagnosis rate at two years follow-up time was 98.5 (95%CI:75.8-121.3) and decreased to 13.4 (95%CI:4.9-21.9) per 100,000 women screened at fifteen years follow-up time (Table 3). Similarly, overdiagnosis rates for women at older screening start ages (52, 54, …, 68) all decreased with longer follow-up time. Overdiagnosis rate was higher for older women than younger women (Table 3). Overdiagnosis rate for women diagnosed at age 50 was 98.5 (75.8-121.3) and 13.4 (4.9-21.9) at two and fifteen years follow-up, respectively. For women diagnosed at age 56 who had three negative mammograms, overdiagnosis rate decreased to 30.6 (23.4-37.8) and 7.9 (3.5-12.4) at two and fifteen years follow-up, respectively (Table 4).

Sensitivity analysis

The sensitivity analysis showed that the overdiagnosis rate was most sensitive to the mean tumour volume doubling time and varied between 5.6 and 33.3 per 100,000 screened women when set at the lower and upper 95%CI limit, respectively (Figure 1, Table S2). However, the tumour volume doubling time of women older than 70 only had a minor effect on overdiagnosis rate. A smaller mean size of self-detected tumours, a lower lifetime risk of developing breast cancer, and 50% uptake were associated with a decreased overdiagnosis rate.

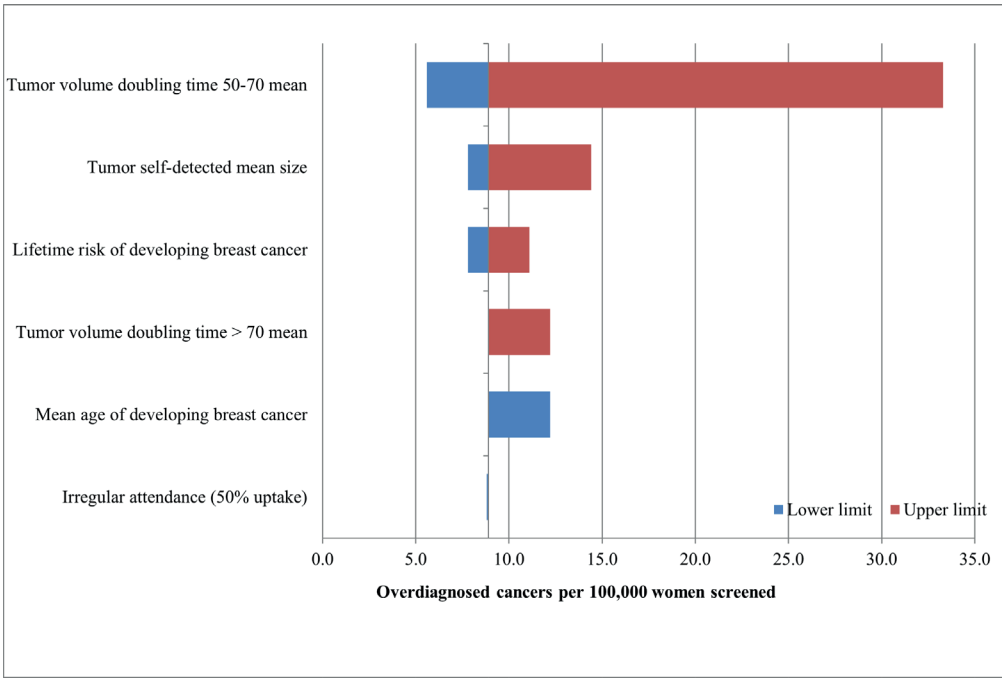

Fig. 1. Sensitivity analysis of overdiagnosis parameters set at lower and upper 95%CI limit.

Discussion

In this study, after the simulation model was successfully calibrated and validated to population-screening in Flanders, we found an overdiagnosis rate of 17.8 invasive breast cancers per 100,000 women screened biennially from age 50 to 68, at a follow-up of fifteen years after screening stops. Overdiagnosis was overestimated at 40.5 per 100,000 women screened using insufficient follow-up time of two years. Overdiagnosis rate for women who started screening at age 68 was nearly three times higher than for women who started

screening at age 50. In addition, for women of different ages at commencement of screening, overdiagnosis decreased with longer follow-up and stabilized at ten-year follow-up. The estimated overdiagnosis rate was most sensitive to changes in tumour volume doubling time, the size of self-detected tumours, and lifetime risk of developing breast cancer.

Our model showed lower overdiagnosis rates for invasive breast cancer with longer follow-up time for all birth cohorts. In previously published studies, for a follow-up time of ten years or more, the published proportion of overdiagnosed invasive breast cancers are generally low, in the range of 1.0% to 3.0% in observed data[17,39] and 0.4 to 4.6% in modeling studies[15,38], which is comparable to our model estimated proportion of overdiagnosed invasive breast cancers of 2.4% at fifteen years follow-up time. For a follow-up time of five years, the published proportion of overdiagnosed invasive breast cancers vary between 14.7% and 56% in observed data[16,19], which is higher than our model's estimated proportion of overdiagnosed cancers at five years of 2.7%. The large variation of published data at short follow-up time epitomizes the impact of the population characteristics and the definition of overdiagnosis, however, the decreased overdiagnosis at longer follow-up time shows the dominant role of the length of follow-up time on the estimation of overdiagnosis in breast cancer screening program.

We found that overdiagnosis was nearly three times higher in women who started screening at age 68 compared to women who started screening at age 50. This observation is new, as overdiagnosis is commonly reported as a point estimate for a whole screened population, independent of age.[5,6,9,15–20] There are some potential explanations for the more pronounced effects of overdiagnosis of invasive breast cancer with a shorter follow-up time in older women. Older women have a higher breast cancer risk and a lower average breast cancer growth rate compared to younger women.[21,22] Because of this higher risk, the incidence is higher among older women and more screen-detected tumours will be found, and because of the lower growth rate, these tumours are less likely to become symptomatic without screening and are more likely to be overdiagnosed. Moreover, older women are more likely to die of competing causes of death such as heart disease, other cancers, and external causes[40,41] than younger women . Therefore, compared to younger women, older women are less likely to be diagnosed with breast cancer during follow-up time after screening stops due to higher risk of competing causes of death and are thus more likely to become overdiagnosed with breast cancer. Change in life expectancy was accounted for in the simulations since life expectancy is incorporated in our model.

We also found that overdiagnosis rate decreased with more previously negative mammograms, and was most evident for prevalence mammography. This is in line with a previous publication from the UK.[42] A strength of this study is that we applied and validated

an already existing and validated model with input parameters that were independently derived from published sources. The model enabled the estimation of overdiagnosis rate via a per woman comparison of women in a screened and unscreened situation. Our estimates can give quantified evidence of overdiagnosis related to the detection of invasive breast cancers by screening and can also quantify the impact of the length of follow-up time on the magnitude of overdiagnosis related to invasive breast cancers. Moreover, our estimated overdiagnosis rates were robust for most model input parameters.

This study has some limitations. First, the number of screen-detected breast cancers was underestimated in older age-groups in the first screening round. This can be caused by an underestimation of the tumour doubling time in older women. The validation results also showed that the simulated number of screen-detected breast cancers was overestimated for younger age groups in the second screening round. This overestimation can be caused by overestimation of tumour doubling time in young women or an overestimation of tumour size at symptoms in this young age-group, or both. The slight underestimation of large-sized cancers in the second screening round could be related to our age dependent tumour volume doubling time model. An underestimation of the variance of cancer growth might cause an underestimation of large-sized cancers. Second, our estimate of overdiagnosis was most sensitive to a change in tumour volume doubling time in women aged 50-70 years old. In our model the tumour growth was modelled as an exponential growth with a log-normal distribution around a mean growth rate per age group. Although the growth characteristics resemble the observed age dependent growth rate of breast cancer[21] only one mean growth rate was used per age group. Extension of our growth model with distributions around slow, medium, and fast growing tumours might therefore yield a more accurate estimation of overdiagnosis in breast cancer screening. Third, we assumed a 100% uptake of screening for our estimation, which is less likely to happen in population screening programs. This, because we aim to quantify overdiagnosis of invasive breast cancer from the perspective of women who will participate in the screening. The overdiagnosis rate with lower screening uptake is expected to be lower than our estimates, which has been verified in the sensitivity analysis. Due to these limitations, point estimates of overdiagnosis rate should be interpretated as approximations, because of the inherent uncertainties of the microsimulation approach. Our results are particularly useful to test multiple scenarios that otherwise would be impossible to test in an observational study.

Overdiagnosis is recognized as the most serious harmful effect of screening.[1,12] It leads to unnecessary physical and mental burden and potential overtreatment of women who would not have been diagnosed with breast cancer in the absence of screening.[1,12] Since overdiagnosis is caused by the detection of cancer that would not have been diagnosed if not screened, the surge of detected cancers in a short term will be largely compensated

by long term follow-up time. Therefore, a long follow-up time is needed to accurately estimate overdiagnosis.[11,14] As pointed out in some studies, the extent of overdiagnosis is overestimated if follow-up time is shorter than the maximum lead time.[11,43] Our results verify that the overdiagnosis rate decreases in the first five years of follow-up. Furthermore, we found that for women who started screening from all different ages, overdiagnosis rates are overestimated with insufficient follow-up time. In addition, the overdiagnosis rate in all ages stabilized at follow-up longer than ten years. Therefore, overdiagnosis of invasive breast cancer should be estimated with at least five years of follow-up and estimates with ten years or longer follow-up will be optimal. For women who started screening at older age (60+), a sufficient follow-up is even more important than for younger women, because overdiagnosis of invasive breast cancer is a higher problem for older women compared to younger ones.

Future efforts are needed to estimate overdiagnosis caused by DCIS. Although there is general consensus that DCIS is an important cause of overdiagnosis, accurate estimation of overdiagnosis from DCIS is difficult, mainly because of the lack of definitive evidence about the probability of progression to invasive breast cancer - this is likely less than 40%.[44] In addition, the longer lead time of DCIS compared to invasive cancer entails different estimation approaches of the two entities.[18] These considerations led to our focus on invasive breast cancer in this study.

Conclusion

Overdiagnosis rates from breast cancer screening are accurately estimated if a sufficient follow-up duration (10 years or longer) is used after screening stops. The risk of an overdiagnosed invasive breast cancer is <1 in 1000 biennially screened women aged 50-69 with a 10-year follow-up time after screening stops. Overdiagnosis of invasive breast cancer is a larger problem for older women compared to younger women. Overdiagnosis decreased with more previously negative mammograms, suggesting that regular biennial screening optimizes trade-off between benefit and harms (specifically overdiagnosis), no screening avoids overdiagnosis but removes benefit, whereas screening irregularly maintains the harms but reduces potential benefit.

Supplementary materials

Breast cancer registry in Flanders

The management of this screening is ensured by the Flemish Center for Cancer Detection (CvKO). The CvKO provides a registry regarding all screening results. On a regular base, this registry is linked to data from the Belgian Cancer Registry (BCR) which provides data on tumor characteristics. This registry is in line with the General Data Protection Regulations.

Sensitivity model: The sensitivity of the simulation model was based on the sensitivity function described by Isheden & Humphreys (2017) as a logistic function of both tumor diameter and percentage density.

$$\textit{Screening sensitivity } (M,D) = \frac{\exp\left(\beta 1+\beta 2d+\beta 3m+\beta 4\frac{m}{d^2}\right)}{1+\exp\left(\beta 1+\beta 2d+\beta 3m+\beta 4\frac{m}{d^2}\right)}$$

The variable ***d*** denotes the diameter of the tumor and the variable ***m*** denotes the percentage density (m, scaled to [0,1]). The value of parameters ***β1, β2, β3, β4*** were derived from the article of Isheden & Humphreys (2017). The percentage density ***m*** was an area percentage density. We derived the volumetric breast density by BI-RADS categories from Mona Jeffreys (2010) then applied the association between the area density and the volumetric density provided by Mona Jeffreys (2010) to transform the volumetric density to the area percentage.

Supplementary table S2 Input parameters of the SiMRiSc model

Parameters		Value (95%CI)				Reference
Risk of developing breast cancer	Cumulative risk at age 70 (%)	9.9 (9.5-10.3)				29
	Mean onset age (years)	67.5 (67.4–67.5)				
	Standard deviation (years)	17.7 (17.6–17.8)				
Tumor growth	Tumor volume doubling time	Days		Geometric mean, log transformed	Standard deviation	21
	<50 years	80		4.38 (3.78–4.99)	0.43	
	50-70 years	157		5.06 (4.80–5.32)	0.17	
	>70 years	188		5.24 (4.79–5.69)	0.23	
Tumor self-detection	Self-detection diameter (cm)	Geometric mean, log transformed		3.0 (2.9–3.1)		31
		Standard deviation		0.65 (0.55–0.74)		
Average life expectancy population (years)		81.42				29,30
Survival rate (5-year relative survival rate of breast cancer patients)	Tumor diameter 5-10 mm	0.96				
	Tumor diameter 10-20 mm	0.93				
	Tumor diameter 20-50 mm	0.85				
Distribution of BI-RADS category	BI-RADS category	a	b	c	d	34–36
	<40 years [%]	4.4	30.2	48.2	17.2	
	40–50 years [%]	5.9	34.1	46.9	13.1	
	50–60 years [%]	8.5	50.3	36.6	4.6	
	60–70 years [%]	14.9	53.4	29.4	2.3	
	>70 years [%]	17.4	54.3	26.2	2.1	
Mammography	Percentage density (m value) per BI-RADS category:	0.06	0.16	0.40	0.83	32
	Sensitivity function (Supplementary material: Sensitivity model)	β1	-4.38			33
		β2	0.49			
		β3	-1.34			
		β4	-7.18			
	Specificity (%)	96.5 (96.0–96.9)				38
Tumor induction risk	Dose (mSv)	3.0 (1.0-5.0)				25,37
	Excess relative risk for breast cancer per Sv	0.51 (0.28-0.83)				
Systematic error (%)		10				Expert opinion

Supplementary table S2 overdiagnosis rate in sensitivity analysis with input parameters set at lower and upper 95%CI limit

Parameter	Number of overdiagnosed		Number of women screened		Overdiagnosed breast cancers per 100,000 women screened once	
	lower limit	upper limit	lower limit	upper limit	lower limit	upper limit
Mean age of developing breast cancer	11	8	90,041	90,060	12.2	8.9
Tumor volume doubling time > 70 mean	8	11	90,060	90,060	8.9	12.2
Lifetime risk of developing breast cancer	7	10	90,215	89,901	7.8	11.1
Tumor self-detected mean size	7	13	90,060	90,060	7.8	14.4
Tumor volume doubling time 50-70 mean	5	30	90,060	90,060	5.6	33.3
Irregular attendance (50% uptake)	4		45,253		8.8	
Base case	8		90,060		8.9	

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CHAPTER 9

GENERAL DISCUSSION

In this chapter, I summarize the most important findings, discuss the key methodological considerations and the implications of the key findings, and provide my final conclusions.

Summary of the main findings of this thesis

This thesis evaluated the benefits and harms of breast cancer screening, focusing on screening participation. The first part, covering **Chapter 2** and **Chapter 3**, evaluated the impact of screening participation on screen-detected and interval breast cancer stage.[1,2] The second part, comprising **Chapter 4**, **Chapter 5**, and **Chapter 6**, evaluated the determinants of non-participation and coverage of breast cancer screening.[3–5] The third part, **Chapter 7** and **Chapter 8**, evaluated the harms of screening due to the overdiagnosis of invasive breast cancer.[6,7]

Chapter 2: association between screening participation and cancer stage at diagnosis

We evaluated the association between the regularity of participation in breast cancer screening and the stage of breast cancer at diagnosis.[1] The participation of all women diagnosed with breast cancer in Flanders between 2001 and 2018 was linked to the stage of breast cancer at the individual level. Regularity of participation was defined based on the number of, and time interval between, mammograms, categorizing all diagnosed women by attendance into four groups: regular, irregular, only once, and never. We then applied multivariable logistic regression models to evaluate the risk of diagnosing early (I–II) or advanced (III–IV) breast cancer among women in these groups. This revealed that irregular screening had a 17% increased likelihood of finding an advanced stage breast cancer than regular screening; moreover, women who only participated once had a more than two-fold increased risk, while never attenders had a more than six-fold increased risk.

Chapter 3: effectiveness of an organized breast cancer screening program

This chapter provided an evaluation of the effectiveness of an organized breast cancer screening program, considering both participation regularity and breast cancer heterogeneity.[2] Data about the cancer diagnosis were linked at the individual level to participation in the organized screening program for all women diagnosed with breast cancer in Flanders between 2008 and 2018. We then calculated the likelihood of diagnosis with early (I–II) and advanced (III–IV) stage breast cancer between patients with screen-detected and interval breast cancer, as well as the likelihood of diagnosis between those screened regularly and irregularly, performing the analyses separately for the different molecular subtypes. Analysis revealed that screen-detected breast cancer had a higher likelihood of diagnosis at an early stage than interval cancer for all but the HER2-positive

breast cancers. The likelihoods of detection for participants diagnosed with luminal and luminal-HER2-positive breast cancers were 1.21 and 1.79 times higher for those seen regularly and irregularly, respectively.

Chapter 4: determinants of non-participation in breast cancer screening

In this systematic review and meta-analysis about the determinants of non-participation in population-based breast cancer screening programs,[3] we excluded data from self-report and opportunistic screening studies to focus on confirmed data from organized screening programs. We found statistically significant associations between non-participation and low income, low education level, living a large distance from the screening unit, being an immigrant, and having a male family doctor. Interestingly, the effect sizes for these determinants were smaller than in other published meta-analyses.

Chapter 5: determinants of organized and opportunistic breast cancer screening coverage

We studied what determined coverage in organized and opportunistic breast cancer screening in Flanders.[5] Publicly available data on the breast cancer screening coverage rate and socioeconomic status (SES) variables were linked at the municipality level, and a generalized linear equation was applied to model the annually collected data regarding coverage and determinants between 2008 and 2016. This revealed a statistically significant association between low SES and high coverage by opportunistic screening. Conversely, low SES was associated with low coverage by organized screening.

Chapter 6: determinants of screening coverage for women in Flanders

Next, we studied the determinants of screening coverage for women in the lowest and highest 10% of coverage groups in Flanders.[4] Publicly available coverage data for organized and opportunistic screening were linked with SES variables at the neighborhood level in 2017 and we applied quantile regression to evaluate how these were associated. We found that low SES was associated with low coverage by organized screening. Both the poorest and the richest neighborhoods were less likely to take part in organized screening, with both coverage rates in the lowest 10%, but only the richest neighborhoods were more likely to take part in opportunistic screening, with coverage in the highest 10%.

Chapter 7: development of a novel sensitivity model for breast cancer screening

This chapter described the development of a novel sensitivity model, as a function of tumor size, for breast cancer screening.[6] Using publicly available tumor size distributions of screen-detected and interval breast cancers in the Dutch population-based breast cancer

screening program, we applied an exponential tumor growth model to back-calculate the size of the screen-detected and interval breast cancers at the time of screening. Screening sensitivity was calculated based on the observed numbers of true positive and false negative cancers, with the result validated by a comparison with published studies identified through a systematic review. We found that the model-estimated sensitivity of screening increased from 0% to 85% for tumor diameters from 2 to 20 mm, respectively, and that an increased tumor volume doubling time was related to low sensitivity. The model-estimated sensitivity compared favorably with studies in the systematic review.

Chapter 8: overdiagnosis of invasive breast cancer in screening

We studied overdiagnosis of invasive breast cancer in the population-based breast cancer screening program in Flanders.[7] We applied the SiMRiSC model using input parameters from the organized breast cancer screening program in this region, and the model was validated by comparing the model-simulated screening outcomes, including the number and size distribution of the screen-detected and interval cancers, to the observed data. In the validated model, we modeled a biennially screened cohort from age 50 to 69 and a non-screened control cohort. Overdiagnosed invasive breast cancers were identified by comparing the number of diagnosed breast cancers in the screened and control cohorts from the start to the end of screening, plus a variable follow-up of 2–15 years. The impact of screening start age on the overdiagnosis estimate was tested by simulating women screened only once at different starting ages. We found the overdiagnosis rate decreased with a longer follow-up time from 40.5 to 17.8 per 100,000 women screened biennially at 2 and 10 years of follow-up, respectively. At the 10-year follow-up, the overdiagnosis rates were 12.3 and 36.7 per 100,000 women screened once at ages 50 and 68 years, respectively.

Key Topics

Mammography is widely used to detect early breast cancer in most high-income countries. Effective mammography screening programs rely on adequate participation rates among invited women,[8–10] and high participation requires that invited women receive good communication of the benefit and harms (specifically overdiagnosis).[11,12] In this thesis, I have covered several key topics regarding the benefits and harms of population-based mammography screening. Here, I reflect on the methodological considerations and implications of the key findings when implementing breast cancer screening.

Reflection on the methodologies used

A strength of this thesis is that we linked mammography use and cancer diagnosis at the individual level, which provides more accurate estimates of effect than aggregated data[13,14]

and avoids the ecological fallacy.[15] The Center for Cancer Detection in Flanders directly measured both screening participation and cancer diagnosis, and we obtained information about opportunistic screening from reimbursement data instead of relying on self-reported data.[16–18] This approach is commonly used in studies of opportunistic screening and prevents the recall bias associated with self-reported data.[19] In addition, we obtained the SES of participants, which is the most important confounding factor in the relationship between participation and cancer diagnosis, and included all confounding factors in stratified analyses and multivariable models.[20,21]

Our data benefited from being collected from all invited or included women in screening over nearly two decades, thereby avoiding selection bias.[22] Sufficient follow-up time was allocated to observe cancer detection in all included women. The stages (based on the available TNM staging guidelines) and molecular biomarkers associated with breast cancer diagnoses were identified from pathological reports.

Another important consideration is the definitions used for participation and coverage. We assessed the coverage rate as the proportion of eligible women covered by screening and the participation rate as the proportion of invited women who attended screening.[23] When a screening program applies limitations in the invitation scheme, the invited population can be different from the eligible population.[24] Therefore, comparison of the participation rate in different countries must also consider the invitation schemes. [25] The difference between these two indicators can be substantial when opportunistic screening is available, as is the case in Flanders, because women screened in this way are not normally invited to organized screening. Furthermore, by using aggregated population data, we have no information on the specific reason why people do not go to the screening.

Finally, we created multiple scenarios to evaluate the impact of two important yet poorly documented factors on the estimates of overdiagnosis. A validated microsimulation model was used to create scenarios that otherwise cannot be observed in real-life situations. For example, we quantified the overdiagnosis of invasive breast cancer in simulated scenarios, revealing a risk of less than 1 case per 1000 women screened. This suggested that overdiagnosis is more attributable to DCIS than to invasive breast cancer. However, this research focused on invasive breast cancer and did not quantify the overdiagnosis related to DCIS, mainly because of the lack of key input data regarding the lifetime progression probability of DCIS to invasive breast cancer.[26,27] Given that DCIS accounts for around 20% of diagnosed breast cancers[28] and that up to 50% of low-grade DCIS are non-progressive[29,30], DCIS is an important source of overdiagnosis and overtreatment.[30] The main challenge in future studies will be to estimate this overdiagnosis related to DCIS.

The role of screening participation regularity in breast cancer screening

Screening has a clear effect in reducing the breast cancer burden for the whole of society. To realize its full potential to detect breast cancer early, however, screening programs require participation levels that are not only sufficient[8–10] but also at the recommended intervals. The screening interval should be determined by the natural history of cancer[31] and is normally shorter than the mean lead time.[32] Given the average time of 157 days for tumor volume doubling in women aged 50–70 years[33] and the 20 mm diameter upper size limit for stage I breast cancer, a maximum 6 times of volume doubling is allowed. Therefore, a maximum 31 month screening interval is suitable. Consequently, most European countries recommend biennial screening for women aged 50–69 years,[34] with triennial screening less common, as is implemented in the UK. Compared with biennial screening, triennial screening for women aged 50–69 years may achieve few additional benefits and introduce fewer harms than biennial screening.[35]

In Chapter 2, we compared never participants with regular participants and found a much larger effect size than in studies comparing never participants with ever participants.[36–40] Added to this, the results in Chapter 3 associated regular participation with a higher likelihood of screen-detected breast cancer that had more favorable characteristics than interval cancers.[41] Overall, these results highlighted the importance of regular participation.

How to engage non-participants in an organized screening program that co-exists with opportunistic screening

People cannot benefit from the mortality reduction associated with breast cancer screening if they do not take part in the screening program. In addition, the price per participant in terms of mammography is low, where the price for the organization is high, so the price per participant overall is high when the number of participants is too low. Therefore, a key issue for the cost-effectiveness of an organized screening program is to engage non-participants.[8–10] In some countries, participants do not join in organized screening for breast cancer, and they are instead referred without symptoms by a medical doctor for mammography; this is called opportunistic screening, and is often used as a strategy to engage non-participants.[42,43]

An advantage of the opportunistic screening approach is that it can provide a demand-orientated screening option for women who may prefer more flexible screening times and individualized services.[43] Our results indeed show that women of high SES take part less in organized screening and more in opportunistic screening. However, opportunistic screening adds an important limitation by potentially reducing uptake in the organized breast cancer screening program and making its less cost-effective. Women

in opportunistic screening must also make an out-of-pocket payment in Flanders, which can be an impediment to screening. Indeed, our results show that women of low SES have low participation in opportunistic screening. Despite comparable effectiveness, opportunistic screening also tends to be more costly for the health care system than organized screening.[10,44] Thus, it may be that the time has come to focus on improving access to organized screening and move away from our current reliance on opportunistic screening to reduce non-participation.

Due to its superior cost-effectiveness, organized screening has prevailed over opportunistic screening in most high-income countries.[42,43] However, organized screening cannot reach women who may experience barriers to screening. As is shown in our results, both the richest and poorest women take less part in organized screening, but only the richest women show a preference to take part in opportunistic screening and the poorest have limited participation. This indicates that organized screening is the key to boosting screening coverage among non-participating women of low SES who are sensitive to cost. In addition, greater effort is needed to reach the women of low SES who may experience barriers to taking part.[3] The low uptake of organized screening services by women of low SES should also trigger reflection about the current recruitment strategy that relies solely on age. Organized screening could be made more flexible to facilitate screening for the richest women who prefer more flexible services.

Mammography programs in most countries recruit women by sending one-size-fits-all invitations via mail,[34,45,46] an approach that may fail to reach women who face barriers to participation.[47,48] In the systematic review in Chapter 4, we found that women were less likely to participate in organized screening if they had low incomes, had low educational attainments, lived far from a screening unit, were immigrants, and had a male family doctor. Offering tailored recruitment strategies, such as sending reminders by telephone,[49] mail,[50,51] and text message,[52] could facilitate their engagement.

Roles of follow-up time and age at screening in estimating overdiagnosis

Overdiagnosis is the major harm of breast cancer screening and needs accurate quantification. Although most agree that detecting DCIS by screening causes overdiagnosis,[28,29] the impact of detecting invasive breast cancer on overdiagnosis remains a matter of debate. Published data on the topic vary significantly[53,54] and offer limited information to help women decide about whether they should participate. Various factors contribute to the large variation in overdiagnosis,[55] with the most well-documented being the definition of overdiagnosis,[56,57] the assumption of incidence trend,[54] and the control group used to identify overdiagnosis.[54] In our study, we addressed two important and

unquantified factors that affect overdiagnosis: the follow-up time after screening and the age of screened women.

Our results showed that overdiagnosis decreased with a shorter follow-up time and stabilized with a longer (≥10 years) follow-up time. In addition, overdiagnosis decreased with longer follow-up times at different starting ages, while older starting ages were associated with more overdiagnosis. These results suggest that ensuring a sufficient follow-up time (≥10 years) is key to obtaining an unbiased estimate of overdiagnosis. Concerning future policy, a single estimate of overdiagnosis can no longer be applied to all women invited for screening.[11,12,58] Instead, the risk of overdiagnosis needs to be tailored by age, with women only given estimates of overdiagnosis based on sufficient follow-up time.

Conclusions

This thesis demonstrated an association between less regular participation in breast cancer screening and significantly lower odds of cancer detection as well as higher odds of advanced stage cancer detection. Regular screening is key to detecting breast cancer at an early stage. However, whereas women of both high and low SES had high non-participation rates in organized screening, it was mostly women of high SES who participated in opportunistic screening. To improve the efficiency of organized screening, we need to evaluate strategies that can reach non-participating women and we must improve recruitment efforts for women of low SES who may face barriers to screening. It was also shown that overdiagnosis was more related to DCIS than to invasive breast cancer, and that estimates of invasive breast cancer overdiagnosis depend on the follow-up time and age of screening. Moving forward, we must ensure a sufficient follow-up time of at least 10 years to obtain unbiased overdiagnosis estimates.

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Appendices

Nederlandse samenvatting

In dit hoofdstuk vat ik de belangrijkste bevindingen samen, bespreek ik de belangrijkste methodologische overwegingen en de implicaties van de belangrijkste bevindingen, en geef ik mijn eindconclusies.

Samenvatting van de belangrijkste bevindingen van dit proefschrift

Dit proefschrift evalueerde de voor- en nadelen van borstkankerscreening, met nadruk op deelname aan screening. Het eerste deel, dat hoofdstuk 2 en hoofdstuk 3 beslaat, evalueerde de impact van deelname aan screening op het stadium van screening-gedetecteerde en intervalborstkanker. Het tweede deel, bestaande uit hoofdstuk 4, hoofdstuk 5 en hoofdstuk 6, evalueerde de determinanten van niet-deelname en de dekking van borstkankerscreening. Het derde deel, hoofdstuk 7 en hoofdstuk 8, evalueerde de nadelen van screening als gevolg van overdiagnose van invasieve borstkanker.

Hoofdstuk 2: verband tussen deelname aan screening en kankerstadium bij diagnose

We evalueerden de associatie tussen de regelmaat van deelname aan borstkankerscreening en het stadium van borstkanker bij diagnose. De deelname van alle vrouwen met borstkanker in Vlaanderen tussen 2001 en 2018 was op individueel niveau gekoppeld aan het stadium van borstkanker. De regelmaat van deelname werd bepaald op basis van het aantal en het tijdsinterval tussen mammogrammen, waarbij alle gediagnosticeerde vrouwen op aanwezigheid in vier groepen werden ingedeeld: regelmatig, onregelmatig, slechts één keer en nooit. Vervolgens hebben we multivariabele logistische regressiemodellen toegepast om het risico op het diagnosticeren van vroege (I-II) of gevorderde (III-IV) borstkanker bij vrouwen in deze groepen te evalueren. Hieruit bleek dat onregelmatige screening 17% meer kans had op het vinden van een vergevorderd stadium van borstkanker dan reguliere screening; bovendien hadden vrouwen die slechts eenmaal deelnamen een meer dan tweevoudig verhoogd risico, terwijl nooit deelnemers een meer dan zesvoudig verhoogd risico hadden.

Hoofdstuk 3: effectiviteit van een georganiseerd bevolkingsonderzoek naar borstkanker

Dit hoofdstuk gaf een evaluatie van de effectiviteit van georganiseerd bevolkingsonderzoek naar borstkanker, rekening houdend met zowel de regelmaat van deelname als de heterogeniteit van borstkanker. Gegevens over de kankerdiagnose werden op individueel niveau gekoppeld aan deelname aan het georganiseerde screeningsprogramma voor alle vrouwen met borstkanker in Vlaanderen tussen 2008 en 2018. Vervolgens berekenden we de kans op diagnose bij vroeg (I–II) en gevorderd (III–IV) stadium van borstkanker

tussen patiënten met screening-gedetecteerde en intervalborstkanker, evenals de waarschijnlijkheid van diagnose tussen degenen die regelmatig en onregelmatig worden gescreend, waarbij de analyses afzonderlijk werden uitgevoerd voor de verschillende moleculaire subtypes. Uit de analyse bleek dat behalve bij de HER2-positieve borstkankers, borstkanker in een vroeg stadium een grotere kans op diagnose had dan intervalkanker. De kans op detectie voor deelnemers met de diagnose luminaal en luminaal HER2 positief borstkanker was respectievelijk 1,25 en 1,79 keer hoger voor degenen die regelmatig en onregelmatig werden gezien.

Hoofdstuk 4: determinanten van niet-deelname aan borstkankerscreening

In deze systematische review en meta-analyse over de determinanten van niet-deelname aan georganiseerde borstkankerscreeningprogramma's, hebben we de data uitgesloten van zelfrapportage- en opportunistische screeningstudies. We vonden statistisch significante associaties tussen niet-deelname en laag inkomen, laag opleidingsniveau, op grote afstand wonen van de screeningseenheid, allochtoon zijn en een mannelijke huisarts hebben. Interessant is dat de effectgroottes voor deze determinanten kleiner waren dan in andere gepubliceerde meta-analyses.

Hoofdstuk 5: determinanten van de dekking van georganiseerde en opportunistische borstkankerscreening

We onderzochten wat de dekkingsgraad in de georganiseerde en opportunistische borstkankerscreening in Vlaanderen bepaalde. Openbaar beschikbare gegevens over de dekkingsgraad van borstkankerscreening en sociaaleconomische status (SES)-variabelen werden gekoppeld op gemeentelijk niveau, en een algemene lineaire vergelijking werd toegepast om de jaarlijks verzamelde gegevens over dekking en determinanten tussen 2008 en 2016 te modelleren. Dit liet een significante associatie zien tussen lage SES en hoge dekking door opportunistische screening. Omgekeerd werd een lage SES geassocieerd met een lage dekking door georganiseerde screening.

Hoofdstuk 6: determinanten van screeningsdekking voor vrouwen in Vlaanderen

Vervolgens bestudeerden we de determinanten van screeningsdekking voor vrouwen in de laagste en hoogste 10% dekkingsgroepen in Vlaanderen. Openbaar beschikbare dekkingsgegevens voor georganiseerde en opportunistische screening werden in 2017 gekoppeld aan SES-variabelen op buurtniveau en we pasten kwantielregressie toe om te evalueren hoe deze verband hielden. We ontdekten dat een lage SES geassocieerd was met een lage dekking door georganiseerde screening. Zowel de armste als de rijkste buurten namen minder vaak deel aan georganiseerde screening, met beide dekkingsgraden in

de laagste 10%, maar alleen de rijkste buurten deden vaker mee aan opportunistische screening, met dekking in de hoogste 10%.

Hoofdstuk 7: ontwikkeling van een nieuw sensitiviteitsmodel voor borstkankerscreening

Dit hoofdstuk beschrijft de ontwikkeling van een nieuw sensitiviteitsmodel als functie van tumorgrootte voor borstkankerscreening. Met behulp van openbaar beschikbare tumorgrootteverdelingen van door screening gedetecteerde en interval borstkankers in het Nederlandse bevolkingsonderzoek, hebben we een exponentieel tumorgroeimodel toegepast om de grootte van de door screening gedetecteerde en intervalborstkankers terug te rekenen naar het moment van screening. Screeningsgevoeligheid werd berekend op basis van het waargenomen aantal echt positieve en fout-negatieve kankers, waarbij het resultaat gevalideerd werd door een vergelijking met gepubliceerde onderzoeken die werden geïdentificeerd via een systematische review. We vonden dat de door het model geschatte gevoeligheid van screening toenam van 0% tot 85% voor tumordiameters van respectievelijk 2 tot 20 mm, en dat een hogere verdubbelingstijd van het tumorvolume verband hield met een lagere gevoeligheid. De door het model geschatte gevoeligheid was gunstig in vergelijking met studies in de systematische review.

Hoofdstuk 8: overdiagnose van invasieve borstkanker bij screening

We bestudeerden overdiagnose van invasieve borstkanker in het bevolkingsonderzoek naar borstkanker in Vlaanderen. We hebben het SiMRiSC-model toegepast met behulp van invoerparameters van het georganiseerde screeningsprogramma voor borstkanker in deze regio, en het model werd gevalideerd door de model-gesimuleerde screeningresultaten, inclusief het aantal en de grootteverdeling van de door screening gedetecteerde en intervalkankers, te vergelijken met de waargenomen data. In het gevalideerde model hebben we een tweejaarlijks gescreend cohort van 50 tot 69 jaar en een niet-gescreend controlecohort gemodelleerd. Overgediagnosticeerde invasieve borstkankers werden geïdentificeerd door het aantal gediagnosticeerde borstkankers in de gescreende en controlecohorten van het begin tot het einde van de screening te vergelijken, plus een variabele follow-up van 2-15 jaar. De impact van de startleeftijd van de screening op de schatting van de overdiagnose is getest door slechts eenmaal gescreende vrouwen op verschillende startleeftijden te simuleren. We vonden dat het percentage overdiagnose afnam met een langere follow-uptijd van 40,5% naar 17,8% per 100.000 vrouwen die tweejaarlijks werden gescreend na respectievelijk 2 en 10 jaar follow-up. Bij de follow-up van 10 jaar waren de overdiagnosepercentages 12,3% en 36,7% per 100.000 eenmaal gescreende vrouwen op de leeftijd van respectievelijk 50 en 68 jaar.

Conclusies

Dit proefschrift toont een verband aan tussen minder regelmatige deelname aan borstkankerscreening en een significant lagere kans op detectie van kanker in de screening en een hogere kans op detectie van kanker in de screening in een gevorderd stadium. Regelmatige screening is daarom essentieel om borstkanker in een vroeg stadium op te sporen. Hoewel vrouwen met zowel een hoge als een lage SES een hoge mate van niet-deelname hebben aan georganiseerde screening, zijn het vooral vrouwen met een hoge SES die deelnemen aan opportunistische screening. Om de efficiëntie van georganiseerde screening te verbeteren, moeten we strategieën evalueren die niet-deelnemende vrouwen kunnen bereiken en moeten we de rekruteringsinspanningen verbeteren voor vrouwen met een lage SES die mogelijk te maken hebben met barrières voor screening. Er werd ook aangetoond dat overdiagnose meer gerelateerd is aan DCIS dan aan invasieve borstkanker, en dat schattingen van overdiagnose van invasieve borstkanker afhangen van de follow-up tijd en de leeftijd van screening. In de toekomst moeten we zorgen voor een voldoende follow-up tijd van ten minste 10 jaar om goede schattingen van overdiagnose te krijgen.

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Lilu Ding is a researcher from China. He studied public health and medicine at Anhui Medical University from September 2008 to June 2013 and received a bachelor's degree in Medicine. He received a master's degree in Medicine from Shandong University. During his study at Shandong University from September 2013 to June 2016, he joined several research projects regarding the rational use of antibiotics in China. From September 2016 to September 2018, he worked as a junior researcher in the Nanjing Drum Tower Hospital, where he joined a project on the evaluation of a landmarking reform case of the public hospital system in China.

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