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## Quantifying independent risk factors for failing to rescreen in a breast cancer screening program in Flanders, Belgium

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### Abbreviations:

BCSP: breast cancer screening program

AUC: area under the curve

ROC: receiver operating characteristic

**Abstract**

**Background** Mammographic screening may reduce breast cancer mortality by about 20%, provided participation is high and women screen regularly. We quantified independent risk factors for failing to rescreen and built a model to predict how rescreening rates change if these risk factors would be modified. **Methods** Multivariate analysis was used to analyze data from a prospective study which included a self-administered questionnaire and rescreening status 30 months after a t0 mammogram, using a random sample of women 50-67 years (Belgium 2010-2013). **Results** A false positive result at the most recent past mammogram (OR = 5.0, 95%CI 3.6-6.8), an interval until new invitation greater than 25 months (OR = 4.8 for >29 months, 95%CI 2.9–8.1), waiting times in the mammography unit >1 hour (OR = 2.1, 95%CI 1.2-3.7) and difficulties in reaching the unit (OR = 2.5, 95%CI 1.4-4.4) were the strongest independent predictors for failing to rescreen. The AUC of the ROC analysis was 0.705 for the model development stage and 0.717 for the validation stage and goodness-of-fit was good. **Conclusions** Maintaining an invitation cycle of maximum 25 months, limiting waiting time in the mammography unit and lowering the number of false positives could increase breast cancer screening compliance.

**Key words:** Breast cancer screening; adherence; risk factors; rescreening

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## Background

The Belgian incidence rate of breast cancer is 178.2/100,000 person years (106.0/100,000 World Standard Population). In Belgium and many other Western style countries breast cancer is the leading cause of cancer death in females, contributing to a large interest in the possibilities for prevention. Mammographic screening has both harmful effects (e.g. overdiagnosis) and benefits (e.g. breast cancer mortality reduction). These have been under intense scrutiny for more than a decade and this debate is unlikely to end soon. Recently a review panel found breast cancer specific mortality can be reduced by about 20% in women over 50 years old invited to screening but the level of participation and rescreening rates are important limitations to accomplishing this [1-4].

European guidelines suggest evaluating rescreening behavior by calculating the percentage of women that rescreen within 30 months of their last mammogram [5]. Literature describes several risk factors for not rescreening: low education [6], low household income [7], infrequent contact with a physician [8-10], little ability to take time off work [11, 12], higher age [9], no personal or familial history of breast problems [4, 13], the absence of a formal reminder system and the presence of financial barriers.

The purpose of this study is to examine and quantify variables which are independently related to rescreening in the Flemish Breast Cancer Screening Program (BCSP) and build a valid prediction model to predict how rescreening rates would change if these risk factors would be influenced.

## Methods

### *Screening in Belgium*

Cancer prevention in Belgium is organized by the three regions. The Flemish region has 6.2 million of Belgium's 10.8 million inhabitants and started a BCSP in compliance with European guidelines in June 2001. In the BCSP all eligible women in the age group 50-69 receive a personalized letter every two years with a set appointment for a screening mammogram which is paid entirely and directly by the healthcare insurance to the mammography unit. The date, time and place of the appointment can easily be changed by phoning a toll free number which results in about 1/3 of all BCSP mammograms being taken on a rescheduled appointment. Women with symptoms or an elevated risk of breast cancer are encouraged to consult a physician rather than participating in the BCSP.

Until June 2011 breast cancer screening was only possible as opportunistic screening which is on prescription only and has a higher self-pay than the BCSP mammogram and must be paid in full at the time of consultation. After reimbursement this involves around 15 to 30 euro of costs for the woman. Opportunistic screening, unlike the BCSP, does not include organized quality control (e.g. double reading), its data are not stored in one central database and it costs more to the healthcare system.

The percentage of women screened in the periods 1999-2000, 2001-2002 and 2006-2007 was 33%, 27% and 21% in opportunistic screening and 0%, 23% and 44% through the BCSP (adding percentages provides total coverage) [7]. Data on the usage of clinical breast exams or self-exam in Belgium are not available but national GP guidelines do not recommend clinical breast exams or self-exam for screening of asymptomatic average risk women, although women are encouraged to develop breast awareness.

### *Study population*

At the time of screening all women are asked to consider giving written informed consent to allow the use of their screening data for scientific research (given by 99.5%). Only women that signed informed consent were candidates for the study. Women were eligible for inclusion in the study if in 2010 they lived in the provinces of *Antwerpen* or *Vlaams-Brabant* and had a BCSP mammogram done in 2010 (n=61,221), a random sample of them was included in the study (n=21,167). Inclusion meant they received a satisfaction questionnaire (see below) together with the invitation for screening. 1,487 women of the random sample (7.0%) were no longer eligible to participate in the BCSP two years after their t0 mammogram (moved out of Flanders, breast cancer diagnosis, died or aged outside the BCSP age-limits). Their answers were needed for representative feedback on client satisfaction for the mammographic units but left out of the analysis. Of the remaining 19,680 women, 6,965 returned the questionnaire (response rate 35.4%).

### *Questionnaire*

The search for a validated satisfaction questionnaire included publications from the present until 20 years ago, supplemented with references that were mentioned in the retrieved articles. No validated satisfaction questionnaire was available in Dutch so we constructed one based on three validated English language questionnaires [8, 14, 15], which were selected because they are culturally appropriate to the Flemish situation. One researcher translated the selected questions into Dutch, after which another researcher performed back translation. To examine the applicability of this preliminary survey it was administered to a group of 9 hospital volunteers who had undergone mammogram in the last year. Several modifications were then made to avoid confusion.

The questions of the final questionnaire can be seen in table 2. The variable *Result of screening of t0 mammogram* had two possible values: false positive recall versus no recall for further assessment (recall rate is the number of women recalled for further assessment as a proportion of all women who had a screening examination). Women with true positive recall were diagnosed with breast cancer and therefore not included in the study. Waiting time for results is defined as the days between screening date and date the result letter is sent. Waiting time in the mammography unit is the time spent in the waiting room of the unit. All satisfaction questions used a 5-point Likert scale except the question on difficulties in reaching the unit (e.g. great distance or transport problems) which used a yes/no option as in the study where it was originally developed. The other independent variables in table 2 are part of the BCSP database.

#### *Database construction*

In July 2013 the BCSP database was linked to the returned questionnaires with the use of a unique identifier which was then removed from the study database. The 2010 mammogram is referred to as the t0 mammogram while a mammogram by the same woman in 2012 or 2013 is referred to as the t1 mammogram. Every woman had 913 days of follow up after her t0 mammogram, at which point rescreening status was determined for each woman. A t1 mammogram taken more than 913 days after the t0 mammogram was not counted towards rescreening status at 30 months.

#### *Analysis*

To evaluate non-response bias we compared characteristics of responders and either non-responders or the women of the sample area depending on whether the variable is available for the non-responders.

The answers to the questionnaire, together with a selection of variables from the BCSP database, were used as independent variables in the multivariate analysis that used rescreening status after 30 months as dependent variable.

Analysis and data storage was done using STATA version 10 (StataCorp., USA). Relationships between two categorical variables were examined with contingency tables using Chi square test and crude OR's with 95% CI. Univariable relationships between continuous variables and outcome were assessed using logistic regression. Variables were all categorized, with grouping of values based on clinical similarity (e.g. age) or similarity of crude OR (e.g. month of invitation, waiting time for result letter). Resulting categories can be found in table 2, with crude OR and 95% CI.

A multiple logistic regression model to predict individual status of rescreening after 30 months was built on a random sample of 2/3 of the data; the remaining 1/3 was used to validate the model. The variables age, education and screening round were always included irrespective of statistical significance since these variables have previously been shown to be clinically important variables to adjust for. Other variables were only candidates for purposeful selection if they had p-values <0.25 in univariable analysis. Whether or not a variable was added to the model was based on the likelihood ratio test with significance set at p<0.01.

The assessment of the resulting model was done by assessing the goodness of fit using the Hosmer-Lemeshow goodness-of-fit statistic and examining the discriminatory accuracy using the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis.

#### *Prediction*

The regression coefficients of the variables in the final model were rounded to 4 decimals and used to create the  $\beta$  of formula 1, which calculates the predicted individual probability ( $p_i$ ) for each patient to rescreen. The rescreening rate in the population was calculated as the arithmetic mean of these individual probabilities. Formula 1 was used to predict the rescreening rate in a situation where the  $X_i$  has been influenced (see example in results, model prediction).

#### **Formula 1 Type of model to predict rescreening status at 30 months after t0 mammogram**

$$\text{logit}(p_i) = \ln(p_i / 1 - p_i) = \beta_0 + \beta_1 X_{1,i} + \beta_2 X_{2,i} + \dots + \beta_m X_{m,i}$$

$p_i$ : predicted probability of rescreening

$\beta$ : coefficient from the model

X: risk factor value

## Results

Table 1 compares responders and non-responders or the women of the sample area, depending on whether the variable was available for the non-responders. We found no differences in age, employment status and recall rate for further assessment. Responders have a slightly higher adherence to rescreening at 30 months (84.4% versus 81.8%,  $p < 0.01$ ) and women with a high level of education were more likely to respond ( $p < 0.01$ ).

### *Descriptive analysis*

The results of the descriptive analysis are shown in table 2 and are not further commented on here. The overall rescreening rate within 30 months was 84.4%, meaning 15.6% of eligible screened women who were in the study did not return for screening.

### *Association analysis*

In the model building stage 4,602 records were used (a random 2/3 sample of all 6,965 available records), the remaining 2,365 were used for model validation. Despite a sometimes strong crude OR the following variables were not included in the model due to statistically insignificant multivariate results: employment status, experienced roughness, whether the women felt free to ask anything, treatment by receptionist and technician, the type of physician who discussed the t0 results with the woman, see table 2.

The strongest independent associations were observed for a false positive result of the t0 mammogram (OR = 5.0, 95% CI 3.6-6.8) and an interval until new invitation that surpasses 25 months (OR = 4.8 for >29 months, 95% CI 2.9 – 8.1). Of the satisfaction variables the strongest associations are waiting times in the mammography unit (OR = 2.1 for >60 minutes, 95% CI 1.2-3.7) and difficulties in reaching the unit (mainly great distance and transportation inconveniences such as few parking spots and difficult public transport) (OR = 2.5, 95% CI 1.4-4.4).

Pain and embarrassment are overall significantly associated (likelihood ratio test) and therefore included but not every sublevel achieves significance due to small numbers in some categories. The oldest age group has an OR of 2.4 (95% CI 1.8-3.2) for not rescreening.

### *Model assessment*

The AUC of the ROC analysis was 0.705 for the model development stage (2/3 of the data) and 0.717 for the validation stage (1/3 of the data). The goodness-of-fit of the model, tested on both development and validation data, was good with non-significant Hosmer-Lemeshow statistic (0.947 and 0.154).

### *Model prediction*

Table 3 shows the predicted rescreening rate ( $p_i$ ) according to the model (see also formula 1) for different situations, first the current distribution of the variable is used, then the  $p_i$  is calculated for the situation where all the women are in the reference category for that variable (while all other variables stay the same). An example is the situation where reaching the unit is no longer a problem for any of the women: the rescreening rates rise from 84.4% to 84.5%, a gain of 0.1%. The largest gain (1.8%) is seen for maintaining an interval of invitation of  $\leq 25$  months. If all of the mentioned variables could be positively influenced (waiting time, reachability, embarrassment, pain, recall rate, interval between invitation and the type of mammographic unit) the rescreening rate is predicted to rise from 84.4% to 91.1%.

## Discussion

### *Risk factor OR*

Strong risk factors for non-adherence to rescreening are a false positive result of the most recent past mammogram (OR = 5.0, 95% CI 3.6-6.8) and waiting times of more than 1 hour in the unit (OR = 2.1, 95% CI 1.2-3.7). This is in line with previous research (13, 16, 17). The level of education is not significantly associated with rescreening which contradicts previous research that shows that low education is correlated with lower rescreening rates [6]. Since women with a higher education are more likely to switch to opportunistic screening [7] and the data of opportunistic screenings are not registered in the BCSP database the two phenomena have probably cancelled each other out. Women in the oldest age group are more than twice as likely not to rescreen, this is in line with previous research [7, 9].

The model (see also formula 1) is used to predict the rescreening rate ( $p_i$ ) for situations where modifiable risk factors are dealt with (see table 3). This shows that influencing risk factors with large OR does not necessarily yield a large gain in rescreening rates. The influence of reducing the number of women that receive a false positive recall after  $t_0$  mx (1.1% increase) is much lower than the size of the OR (5.0) would lead one to expect, this is due to the fact that false positive recall is relatively uncommon (4.0%), the % increase will be larger in settings with higher false positive recall. Lowering false-positives is a trade off with the increase of interval cancers (a primary breast cancer diagnosed in a woman in the interval between her last negative screening and her next invitation to screening) and should therefore be done using intensive feedback to radiologists about the outcome of the mammograms to minimize the chances of increasing the number of interval cancers. Women who are invited after 25 months are less likely to take up the invitation, possibly because they have entered into opportunistic screening by then. Mammography units that are privately owned have a markedly lower rescreening percentage, raising the question whether these women are more likely to switch to opportunistic screening.

### *Strengths and weaknesses*

Selection bias due to non-response is a possibility in our study because the questionnaire had an incomplete response. We attempted to evaluate whether our respondents are representative of the sample (detect selective non-response) by comparing the distribution of several characteristics between responders and non-responders.

We found no differences for age, recall for further assessment and work status while there were differences in adherence to screening and education. However, given the size of our study a difference can reach statistical significance without being clinically relevant. We conclude that selection bias is probably present but likely to be limited, meaning the descriptive results are biased to a certain extent while there may also be some overestimated or underestimated OR.

Measurement bias on data from the BCSP database is considered to be extremely low thanks to an important number of automated inconsistency checks that are performed when the data are entered. We attempted to limit measurement bias for the questionnaire data by basing our Dutch questionnaire on several English language questionnaires and by using front and back translation in combination with a small qualitative analysis of the resulting questionnaire. It cannot be excluded that the translation caused a change in validity of the questions, but the fact that the answers have a similar distribution in similar research is an indication that measurement bias of the questionnaire is limited. The ASE model was considered for the construction of the survey but was not used, some of the reasons for this is that we focused on the experience in the mammographic unit, and social support variables are very difficult to modify (we were looking to find ways to improve rescreening rates). Instead a selection was made of those variables that are modifiable to small adaptations in the screening process, or important risk factors based on an extensive literature search. Our final model has a good AUC and goodness-of-fit making prediction possible [19]. Model assessment also shows that there must be additional variables that influence adherence which we did not include in the model. Such factors could include: discouraging physician recommendations [17, 20], dissatisfaction with the method used to communicate results [18], inability to get a mammogram appointment at a convenient hour and a woman's cancer knowledge [11, 12, 20].

### **Conclusions**

We quantified significant risk factors for non-adherence to breast cancer rescreening and constructed a valid prediction model that has good fit although it also shown there are variables that play a role in rescreening behavior that were not included in our study. Rescreening rates can be increased by keeping the invitation interval close to 24 months, reducing the occurrence of false positive results in the previous round and maintaining waiting times in units <20 minutes. Such measures will increase the rescreening rates and thereby optimize the benefits of mammographic screening while they also reduce disadvantages of screening such as unnecessary biopsy, anxiety and discomfort.

### **Conflict of interest statement**

None to declare

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