



## Breast cancer detection risk in screening mammography after a false-positive result

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### ABSTRACT

**Background:** False-positives are a major concern in breast cancer screening. However, false-positives have been little evaluated as a prognostic factor for cancer detection. Our aim was to evaluate the association of false-positive results with the cancer detection risk in subsequent screening participations over a 17-year period. **Methods:** This is a retrospective cohort study of 762,506 women aged 45–69 years, with at least two screening participations, who underwent 2,594,146 screening mammograms from 1990 to 2006. Multilevel discrete-time hazard models were used to estimate the adjusted odds ratios (OR) of breast cancer detection in subsequent screening participations in women with false-positive results. **Results:** False-positives involving a fine-needle aspiration cytology or a biopsy had a higher cancer detection risk than those involving additional imaging procedures alone (OR = 2.69; 95%CI: 2.28–3.16 and OR = 1.81; 95%CI: 1.70–1.94, respectively). The risk of cancer detection increased substantially if women with cytology or biopsy had a familial history of breast cancer (OR = 4.64; 95%CI: 3.23–6.66). Other factors associated with an increased cancer detection risk were age 65–69 years (OR = 1.84; 95%CI: 1.67–2.03), non-attendance at the previous screening invitation (OR = 1.26; 95%CI: 1.11–1.43), and having undergone a previous benign biopsy outside the screening program (OR = 1.24; 95%CI: 1.13–1.35). **Conclusion:** Women with a false-positive test have an increased risk of cancer detection in subsequent screening participations, especially those with a false-positive result involving cytology or biopsy. Understanding the factors behind this association could provide valuable information to increase the effectiveness of breast cancer screening.

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## 1. Introduction

One of the major concerns in breast cancer screening is the false-positive result. The negative effects of a positive mammographic reading in which cancer is excluded after additional evaluation include psychological [1] and behavioral consequences to the screened women [2], as well as additional physician visits, diagnostic tests, and excision biopsies [3,4].

The widespread adoption of breast cancer screening programs involves screening thousands of women periodically, of whom a large number will have a positive mammographic reading requiring additional evaluation. The estimated proportion of

women with a false-positive result after ten screening participations ranges from 20% to 32% in Europe [5–7] and around 49% in the USA [8]. If the false-positive test involves cytology or a biopsy, variability in the estimations increases substantially, ranging from 1.7% to 5% in Europe [5,7], and 18.6% in the USA [8]. However, a negative result after additional evaluation does not necessarily indicate the absence of a benign lesion or a suspicious mammographic pattern.

The dissemination of screening mammography has increased the number of women with radiological abnormalities or benign breast lesions, although there is no general agreement for the follow-up of these women in the screening context. In most population-based screening programs women with a false-positive result follow the same screening recommendations as those with a negative mammographic reading [9]. However, benign breast lesions are a known risk factor for subsequent breast cancer [10,11], and women with benign breast surgery have lower sensitivity at screening [12]. Indeed, the presence of previous

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benign breast lesions is a commonly included variable in the models assessing individual breast cancer risk, along with other factors such as the use of hormone replacement therapy (HRT) and a familial history of breast cancer [13–15].

Although several basic aspects of false positives and their effects have previously been studied, the association between false-positive results and detection of breast cancer in subsequent screening participations has been little studied [16–20]. Most of these studies had a small sample size and a short follow-up time, or had no information on whether the false-positive result involved a cytology examination or biopsy.

In the context of population-based screening programs, in which large cohorts of women are sequentially invited for a mammographic test over a time span of 20 years, the long-term follow-up of women with false-positive results could enhance the prediction of breast cancer risk [13,15]. This information might be useful to improve the effectiveness of breast cancer screening programs by encouraging women with false-positive results to return for further screening.

The aim of this study was to evaluate the association of a false-positive result with risk of breast cancer detection in a cohort of screened women over a sequence of routine screening participations.

## 2. Methods

### 2.1. Setting and study population

The study sample was drawn from a retrospective cohort study of screened women, conducted to evaluate the cumulative risk of a false-positive result over ten sequential screening participations [7]. Briefly, all women aged 45–69 resident in Spain are actively invited to participate in a population-based screening program every 2 years. Population-based breast cancer screening in Spain started in 1990 and became nationwide in 2006. Data from eight regions, covering 44% of the Spanish target population, were collected for this study. Each region has one or several radiology units that perform screening [21]. Breast cancer screening in Spain follows the European Guidelines for Quality Assurance in Mammographic Screening [9].

Information was obtained from 945,789 women who had undergone at least one screening mammogram between March 1990 and December 2006. These women underwent 2,777,429 screening mammograms in any of the 45 radiology units of the eight participating regions that routinely collected information on the women's personal characteristics. The study was approved by the Mar Teaching Hospital Research Ethics Committee.

### 2.2. False-positive results, cancer detection and women's personal characteristics

Women with a positive mammographic reading are recalled for additional evaluation to exclude malignancy. The diagnostic work-up took place within a maximum of 2 months after the screening test. Some women with a probably benign result at mammographic reading are referred for an intermediate mammogram at 6 or 12 months before the interval corresponding to the normal sequence (early recall) [22].

A positive result in the screening test was considered a false-positive result if, after additional evaluation, breast cancer was not diagnosed. Additional evaluation may include additional imaging procedures (additional mammography, magnetic resonance imaging, and ultrasonography), cytology (fine-needle aspiration cytology), or biopsy (core or open biopsy). A definitive diagnosis of breast cancer was always histopathologically confirmed (invasive carcinoma or carcinoma ductal in situ). If cancer was excluded after

additional evaluation, women were routinely invited to participate in the screening program 2 years after the previous screening invitation. No information was available on cancers diagnosed as interval cancers or after women left the screening program.

Information on women's characteristics was obtained by a face-to-face interview performed by a trained health professional at the time of each screening mammogram. This information included the women's age, HRT use (present use or in the previous 6 months), menopausal status (pre- or postmenopausal), previous benign biopsy outside the screening program, and first-degree familial history of breast cancer.

### 2.3. Statistical analysis

The cancer detection rates were calculated as the number of breast cancers detected at screening divided by the number of screened women. The odds ratios (OR) and the 95% confidence intervals (95% CIs) for the association between false-positive results and the risk of cancer detection in subsequent screening participations were estimated with discrete time-hazard models. These models use a logistic regression approach to compute these particular survival models with discrete time intervals [23,24]. The event of interest was whether or not cancer was detected at a routine screening invitation. The probability of a cancer being detected at a routine screening invitation ( $\pi(x)$ ) was expressed as  $\ln(\pi(x)/1 - \pi(x)) = \alpha_i D_i + \beta_j X_j$ , where  $\pi(x)$  is estimated by means of the logit function, like any other logistic regression model.  $D_i$  corresponds to the time indicators: one for each woman's screening participation (first screening, second screening, etc.).  $D_i$  equals 1 if the woman has performed her  $i$ th screening, and is 0 otherwise. The coefficients of the time indicators are expressed by  $\alpha_i$  and are the intercepts in the model (multiple intercept model). As in any other regression model  $X_j$  is the  $j$ th study factor (i.e. first-degree familial history of breast cancer, attended previous screening invitation, etc.), and  $\beta_j$  is the estimated coefficient for the associated study factor. As cancers detected at first screening would not have a previous false-positive result in the screening setting, first screens were censored to compute the regression model estimates, as they would underestimate the risk.

Simple and multivariate models were used to estimate the individual and simultaneous effect of all predictors. The multivariate models included the women's personal variables (age, HRT use, menopausal status, previous benign biopsy outside the screening program, a first-degree family history of breast cancer), whether or not the woman attended her previous screening invitation, and the presence of a false-positive result in any previous screening participation. In addition, the multivariate models included a period effect (calendar years), as the start date of the radiology units differed, and a random effect component defined by the radiology units, because of the correlation among screening tests performed in the same radiology unit. Residual pseudo-likelihood estimation was used in all models by means of the GLIMMIX procedure in SAS 9.1.2 (SAS Institute, Cary, NC).

In further analyses, we tested for interactions between false-positive results and menopausal status, HRT use, family history of breast cancer, and a previous benign biopsy outside the screening program. For simplicity in the interpretation, we performed a stratified analysis for those women's characteristics showing a statistically significant interaction with false-positive results. Besides, to study whether the number of screening rounds since the false-positive test had an effect on the breast cancer risk, we analyzed whether the false-positive test occurred in the previous screening round (2 years) or two or more screenings in advance ( $\geq 4$  years).

Finally, we studied whether the cytologies and biopsies carried out to exclude malignancy were associated with a differential

cancer detection risk. A regression model was computed that included the additional imaging procedures, cytologies, and biopsies as independent categories.

### 3. Results

Of the 945,789 women who had undergone at least one screening mammogram, we excluded information from 183,283 women (19.4%) who had participated in only one screening round and could not be followed up over subsequent screening rounds. We analyzed information from 762,506 women who had at least two screening participations, who underwent 2,594,146 mammographic screening tests between 1990 and 2006. Average (standard deviation) screening participations per woman was 3.70 (1.60); 73% of women had undergone three or more screening mammograms, while 25.5% had at least five screenings.

Overall, the cancer detection rate in subsequent screenings observed was 2.89 cases per 1000 screening mammograms (Table 1). The cancer detection rate for women with a previous false positive involving an additional imaging procedure and those involving a cytology or biopsy was 4.53 and 7.09 cases per 1000 screening mammograms, respectively. Other factors associated with a higher detection rate were a first-degree family history of breast cancer, non-attendance at the previous screening invitation, having experienced a benign biopsy outside the screening program, older age, and post-menopausal status.

False positives showed an increased cancer detection risk in subsequent screening participations. False positives involving a

cytology or biopsy were associated with a significantly higher risk of cancer detection than false positives leading to additional imaging procedures (OR = 2.69; 95%CI: 2.28–3.16 and OR = 1.81; 95%CI: 1.70–1.94, respectively) (Table 2). A higher cancer detection risk was also observed in the oldest women (OR = 1.84; 95%CI: 1.67–2.03), women with a first-degree familial history of breast cancer (OR = 1.65; 95%CI: 1.52–1.79), those not attending the previous screening invitation (OR = 1.26; 95%CI: 1.11–1.43), and those with a previous benign biopsy outside the screening program (OR = 1.24; 95%CI: 1.13–1.35). Of all the factors studied, a previous false-positive result, independently of the additional procedure involved (additional imaging, cytology or biopsy), showed the highest risk of cancer detection (OR = 1.89; 95%CI: 1.77–2.01) (data not shown).

The stratified analyses showed a stronger association of false positives involving a cytology or biopsy with the risk of cancer detection in women with a familial history of breast cancer compared with that in women without a familial history of breast cancer (OR = 4.64; 95%CI: 3.23–6.66, and OR = 2.41; 95%CI: 2.00–2.89, respectively) (Table 3). No differences among women with a familial history of breast cancer were observed for women with a false positive involving additional imaging procedures. None of the other women's characteristics tested for an interaction showed a statistically significant difference.

Fig. 1 shows that false positives after additional imaging procedures or after cytology or biopsy had an increased cancer

**Table 1**  
Number of cancers detected and cancer detection rates in subsequent screens for the women's characteristics studied.

Variable	Subsequent screens (N)	Cancers (N)	Rate <sup>a</sup> (95%CI)
	1,963,225	5670	2.89 (2.81–2.96)
Previous false-positive <sup>b</sup>			
Never	1,663,403	4256	2.56 (2.48–2.64)
Additional imaging	278,081	1261	4.53 (4.28–4.78)
Cytology or biopsy	21,588	153	7.09 (5.97–8.21)
Attended previous screening invitation			
Yes	1,896,407	5410	2.85 (2.78–2.93)
No	66,818	260	3.89 (3.42–4.36)
Age (years)			
45–49	177,671	333	1.87 (1.67–2.08)
50–54	467,619	1036	2.22 (2.08–2.35)
55–59	558,354	1569	2.81 (2.67–2.95)
60–64	514,556	1762	3.42 (3.26–3.58)
65–70	245,025	970	3.96 (3.71–4.21)
HRT <sup>c</sup>			
No	1,743,323	5071	2.91 (2.83–2.99)
Yes	219,902	599	2.72 (2.51–2.94)
Menopausal status			
Menopausal	1,656,585	5025	3.03 (2.95–3.12)
Premenopausal	306,640	645	2.10 (1.94–2.27)
First-degree family history of breast cancer			
No	1,817,823	4989	2.74 (2.67–2.82)
Yes	145,402	681	4.68 (4.33–5.03)
Previous benign biopsy outside screening			
No	1,826,679	5139	2.81 (2.74–2.89)
Yes	136,546	531	3.89 (3.56–4.22)

95%CI=95% confidence interval.

<sup>a</sup> Rate is presented as number of cancers per 1000 screening mammograms.

<sup>b</sup> Previous false-positive: at least one false-positive result in previous screening rounds.

– Never: women who had never experienced a false-positive result.

– Additional imaging: a false-positive involving only an additional mammogram, or a magnetic resonance imaging scan, or an ultrasound scan.

– Cytology or biopsy: a false positive involving fine-needle aspiration cytology, or core biopsy, or open biopsy. 95%CI=95% confidence interval.

<sup>c</sup> HRT: hormone replacement therapy use at the time of the mammogram or in the previous 6 months.

**Table 2**

Estimated odds ratios (OR) from the multiple regression model for the association (non-adjusted and adjusted) between women's characteristics and the risk of cancer detection in subsequent screening participations.

Risk factor	Subsequent screens (N)	OR (95%CI)	
		Non-adjusted <sup>a</sup>	Adjusted <sup>b</sup>
Previous false-positive <sup>c</sup>			
Never	1,663,403	Ref	Ref
Additional imaging	278,013	1.73 (1.62–1.85)	1.81 (1.70–1.94)
Cytology or biopsy	21,809	2.89 (2.48–3.37)	2.69 (2.28–3.16)
Attended previous screening invitation			
Yes	1,896,407	Ref	Ref
No	66,818	1.42 (1.25–1.61)	1.26 (1.11–1.43)
Age			
45–49	177,671	0.83 (0.73–0.94)	0.83 (0.73–0.95)
50–54	467,619	Ref	Ref
55–59	558,354	1.27 (1.18–1.38)	1.30 (1.20–1.42)
60–64	514,556	1.55 (1.43–1.68)	1.62 (1.49–1.77)
65–70	245,025	1.78 (1.63–1.95)	1.84 (1.67–2.03)
HRT <sup>d</sup>			
No	1,743,323	Ref	Ref
Yes	219,902	0.93 (0.86–1.02)	0.96 (0.88–1.04)
Menopausal status			
Menopausal	1,656,585	Ref	Ref
Premenopausal	306,640	0.71 (0.65–0.77)	0.92 (0.83–1.02)
First-degree family history of breast cancer			
No	1,817,823	Ref	Ref
Yes	145,402	1.69 (1.56–1.84)	1.65 (1.52–1.79)
Previous benign biopsy outside screening			
No	1,826,679	Ref	Ref
Yes	136,546	1.38 (1.26–1.51)	1.24 (1.13–1.35)

95%CI=95% confidence interval.

<sup>a</sup> Analysis adjusted by women's screening participation.

<sup>b</sup> Multivariate analysis adjusted by women's screening participation, screening period (years), radiology unit (random effect), and all other factors in the table.

<sup>c</sup> Previous false-positive: at least one false-positive result in previous screening rounds.

– Never: women who had never experienced a false-positive result.

– Additional imaging: a false-positive involving only an additional mammogram, or a magnetic resonance imaging scan, or an ultrasound scan.

– Cytology or biopsy: a false positive involving fine-needle aspiration cytology, or core biopsy, or open biopsy.

<sup>d</sup> HRT: hormone replacement therapy use at the time of the mammogram or in the previous 6 months.

**Table 3**  
Estimated odds ratios (OR) from the multiple regression model for the association between false-positive results and subsequent breast cancer detection risk by the presence or absence of a first-degree familial history of breast cancer.

Previous false-positive <sup>a</sup>	Women with a first-degree family history of breast cancer			Women without a first-degree family history of breast cancer		
	Subsequent screens (N)	Cancer (N)	OR (95%CI) Adjusted <sup>b</sup>	Subsequent screens (N)	Cancer (N)	OR (95%CI) Adjusted <sup>b</sup>
Never	119,782	478	Ref	1,543,621	3778	Ref
Additional imaging	23,859	170	1.82 (1.51–2.18)	254,154	1091	1.81 (1.69–1.95)
Cytology or biopsy	17,961	33	4.64 (3.23–6.66)	20,048	120	2.41 (2.00–2.89)

<sup>a</sup> Previous false-positive: at least one false-positive result in previous screening rounds.

– Never: women who had never experienced a false-positive result.

– Additional imaging: a false-positive involving only an additional mammogram, or a magnetic resonance imaging scan, or an ultrasound scan.

– Cytology or biopsy: a false-positive involving fine-needle aspiration cytology, or core biopsy, or open biopsy.

<sup>b</sup> Multivariate analysis adjusted by women's screening participation, screening period (years), radiology unit (random effect), whether or not the woman attended the previous screening invitation, age at screening, hormone replacement therapy use, menopausal status, and previous benign biopsy outside screening.

detection risk, independently of whether the false-positive test occurred in the previous screening round or two or more screenings in advance. False-positive tests experienced in the previous screening round were significantly associated with a higher cancer detection risk than those experiencing two or more screenings in advance ( $P = 0.025$  and  $P = 0.045$ , for false-positive test after additional imaging procedures and after cytology or biopsy, respectively).

The association between the type of additional procedure carried out in the process leading to the false-positive test and the cancer detection risk is shown in Fig. 2. No differences were found in the cancer detection risk between false positives involving a

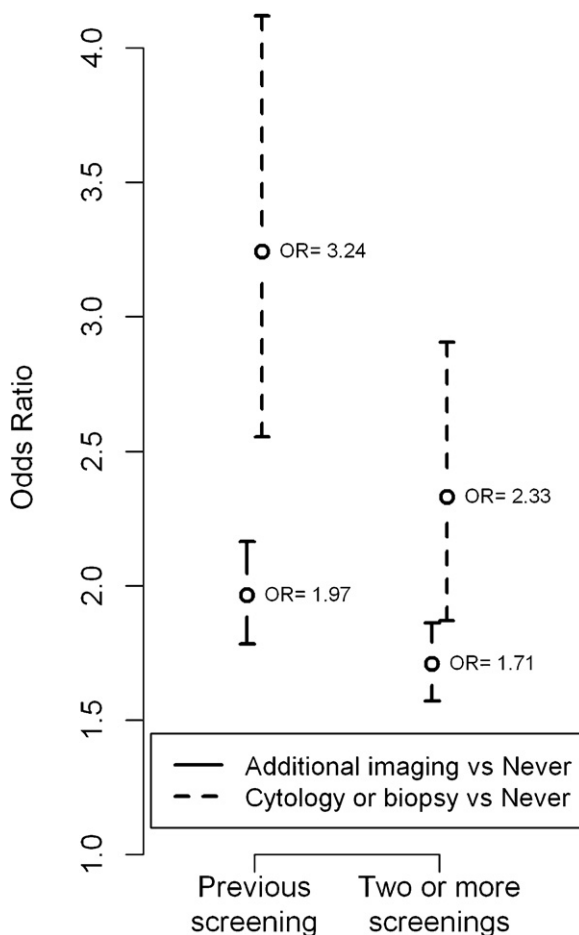
cytology and those involving a biopsy (OR = 2.95; 95%CI: 2.34–3.71, and OR = 2.72; 95%CI: 2.11–3.52, respectively) ( $P = 0.90$ ). False positives leading to additional imaging procedures had a significantly lower cancer detection risk (OR = 1.75; 95%CI: 1.63–1.88) than those involving cytology or a biopsy ( $P < 0.001$  and  $P = 0.005$ , respectively).

#### 4. Discussion

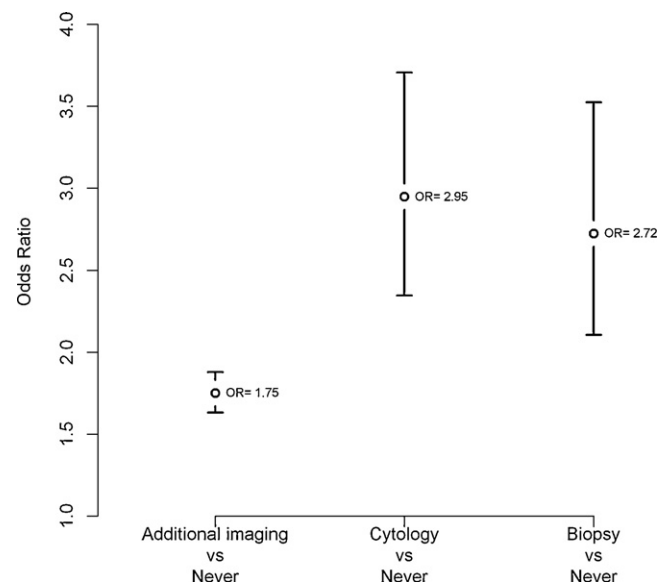
We observed an increased risk of breast cancer detection in women with a previous false-positive test in mammographic screening. Women with a false positive involving cytology or biopsy had a higher risk of cancer detection than those with a false positive involving only an additional imaging procedure. This risk remained significantly higher 4 years or more after the false-positive test. The cancer detection risk increased substantially if women with a cytology or biopsy had a familial history of breast cancer.

The increased cancer detection risk in women with a false-positive test observed in this study is in agreement with the results of previous studies. In a recent study, Euler-Chelpin et al. found an RR = 1.67 of breast cancer diagnosis after a false-positive test [16]. McCann et al. found an OR = 2.15 of cancer detection at the second screen in women with a false-positive test at the first screen [18].

A false-positive test in previous screening rounds is not in itself a risk factor for breast cancer. Some authors have reported false negatives in women undergoing additional evaluation after a



**Fig. 1.** Adjusted odds ratios (OR) for the cancer detection risk depending on whether the false-positive test occurred in the previous screening round or two or more screenings in advance.



**Fig. 2.** Adjusted odds ratios (OR) for the cancer detection risk depending on the type of additional procedure leading to the false-positive test.

positive mammographic reading [18,25–27]. However, in agreement with the study of Euler-Chelpin et al., the cancer detection risk remained significantly higher 4 years or more after the false-positive test [16]. Besides, cancers missed at additional evaluation represent a small proportion of the whole [25], which could only partially explain the association between false-positive tests and the cancer detection risk in subsequent screening participations.

Women with a recommendation for additional evaluation are a specific subgroup of women with mammographic abnormalities. The absence of malignancy does not indicate the absence of benign abnormalities, especially in women recalled for a cytology examination or biopsy. A previous benign breast lesion is a known breast cancer risk factor [10,11,28] and is commonly included in models predicting breast cancer risk. However, few studies have assessed the impact of previous benign lesions in the context of breast cancer screening, in which non-symptomatic women are routinely evaluated. In our analyses, false positives involving a cytology examination or biopsy had an increased cancer detection risk (OR = 2.95 and OR = 2.72, respectively) compared with additional imaging procedures (OR = 1.75). This association was stronger than any other factor analyzed in the study, most of which are usually included in predictive models, such as a first-degree family history of breast cancer, older age, or a previous benign biopsy outside screening.

The risk of cancer detection after a false-positive test involving a cytology examination or biopsy was higher in women with a first-degree familial history of breast cancer (OR = 4.64). This differential effect could be partially explained by the presence of unknown genetic factors or malignant precursors in these women, as well as shared lifestyle and environment, which would involve prognostic factors for benign breast disease to develop into a malignant lesion [11]. In contrast with other studies [17], we found no significant differences in premenopausal women after adjusting for all the other study factors.

We analyzed information from a wide retrospective cohort over a 17-year period, which enabled us to ascertain the risk over a series of sequential screening participations. The wide spectrum of information analyzed – integrating information from several radiology units with different screening protocols – strengthens the consistency of the associations found, independently of possible differences in screening practice or the period analyzed. Moreover, the associations found were observed after adjustment was made for possible confounders, and in the stratified analysis. Nevertheless, our study also has some limitations. We performed specific analyses to outline possible causes for the association studied, which suggested some possible underlying reasons. Further studies are required to confirm the suggested hypothesis. No information was available on breast density, which could be associated with both an increased false-positive risk and an increased breast cancer risk. Previous studies have suggested that the association between previous false positives and cancer detection is independent of breast density [17].

The information provided in this study could be useful to increase the effectiveness of breast cancer screening programs if several surveillance strategies are rethought and defined taking into account personal factors related to breast cancer risk [29], including the results of the screening test. Women with a false-positive result should be encouraged to return for further screening as they have an increased cancer detection risk, and a decreased re-attendance probability [2]. Currently, the quality guidelines [9] define the target population for screening only by women's age and include women who may have very different breast cancer risks in the same target groups. In the actual debate about the effectiveness of breast cancer screening it seems straightforward to consider future screening strategies according

to the breast cancer risk. Personalizing strategies would increase the positive and negative predictive values of mammographic screening, which in turn would enhance its effectiveness. Some studies have provided evidence in this regard [29].

In conclusion, our results showed a strong association between the presence of a false-positive test and the risk of cancer detection in subsequent screening participations. The association was stronger in false-positives involving a cytology examination or biopsy, and in women with a family history of breast cancer. Previous false-positive tests were a better predictor of cancer detection in subsequent screens than older age, a previous benign biopsy outside screening, or a family history of breast cancer alone. In the context of mammographic screening, in which large cohorts of women are assessed every 2 years, this personalized risk information could be useful to improve the effectiveness of breast cancer screening by emphasizing the need for return for further screening in women with false-positive results.

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### Conflict of interest

The authors declare that they have no conflict of interest.

### Appendix

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