

Readmissions and complications in breast ductal carcinoma in situ: A retrospective study comparing screen- and non-screen-detected patients

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Julieta Politi^{1,2}, María Sala^{1,3,4} , Laia Domingo^{1,3}, María Vernet-Tomas⁵, Marta Román^{1,3}, Francesc Macià¹ and Xavier Castells^{1,3}

Abstract

Objective: Population-wide mammographic screening programs aim to reduce breast cancer mortality. However, a broad view of the harms and benefits of these programs is necessary to favor informed decisions, especially in the earliest stages of the disease. Here, we compare the outcomes of patients diagnosed with breast ductal carcinoma in situ in participants and non-participants of a population-based mammographic screening program.

Methods: A retrospective cohort study of all patients diagnosed with breast ductal carcinoma in situ between 2000 and 2010 within a single hospital. A total of 211 patients were included, and the median follow-up was 8.4 years. The effect of detection mode (screen-detected and non-screen-detected) on breast cancer recurrences, readmissions, and complications was evaluated through multivariate logistic regression analysis.

Results: In the majority of women, breast ductal carcinoma in situ was screen-detected (63.5%). Screen-detected breast ductal carcinoma in situ was smaller in size compared to those non-screen-detected (57.53% < 20 mm versus 78.03%, $p=0.002$). Overall, breast-conserving surgery was the most frequent surgery (86.26%); however, mastectomy was higher in non-screen-detected breast ductal carcinoma in situ (20.78% versus 9.7%, $p=0.024$). Readmissions for mastectomy were more frequent in non-screen-detected breast ductal carcinoma in situ. Psychological complications, such as fatigue, anxiety, and depression, had a prevalence of 15% within our cohort. Risk of readmissions and complications was higher within the non-screen-detected group, as evidenced by an odds ratio = 6.25 (95% confidence interval = 1.95–19.99) for readmissions and an odds ratio = 2.41 (95% confidence interval = 1.95–4.86) for complications.

Conclusions: Our findings indicate that women with breast ductal carcinoma in situ breast cancer diagnosed through population-based breast cancer screening program experience a lower risk of readmissions and complications than those diagnosed outside these programs. These findings can help aid women and health professionals make informed decisions regarding screening.

Keywords

breast ductal carcinoma in situ, hospital readmission, mastectomy, patient-relevant outcome, screening

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¹Department of Epidemiology and Evaluation, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

²Preventive Medicine and Public Health Training Unit, Parc de Salut Mar-Pompeu Fabra University-Agència de Salut Pública de Barcelona (PSMar-UPF-ASPB), Barcelona, Spain

³Research Network on Health Services in Chronic Diseases (REDISSEC), Barcelona, Spain

⁴Universitat Autònoma de Barcelona, Barcelona, Spain

⁵Breast Surgery, Obstetrics and Gynaecology Department, Hospital del Mar, Barcelona, Spain

Corresponding author:

María Sala, Department of Epidemiology and Evaluation, Hospital del Mar Medical Research Institute (IMIM), Passeig Marítim, 25-29, 08003 Barcelona, Spain.

Email: MSalaSerra@parcdesalutmar.cat



Introduction

Breast cancer (BC) survival has notably improved over the past few decades, partly because of the effectiveness of population-wide mammographic screening programs. These programs aim to detect early-stage BC, when treatment response is highest, providing a survival advantage compared to clinically detected patients and favoring less invasive treatment.¹ Most tumors identified through screening programs are early-stage BCs.² Of these, breast ductal carcinoma in situ (DCIS) represents 20% of lesions.¹

In general, women treated for DCIS have a relatively low BC-specific mortality and a normal life expectancy.^{2,3} However, there has recently been much controversy surrounding to which extent the diagnosis and treatment of DCIS prevent future invasive BC and there is a growing concern for overdiagnosis and overtreatment.

To ascertain the effectiveness of screening programs, some studies have compared the effect of screening on DCIS, being mortality and disease-free survival as their main focus.⁴ However, other outcomes that may be of significant interest from a patient's point of view, such as treatment patterns, hospital readmissions, or other complications, have been less evaluated, and there is limited observational information regarding complications for BC in general.⁵ Furthermore, to date, no previous study has evaluated complications according to screening status for DCIS.

Our study aimed to compare readmissions, complications, and recurrences of patients diagnosed with breast DCIS in participants and non-participants of a population-based mammographic screening program.

Materials and methods

Study population

Women diagnosed with DCIS as a first BC event between 2000 and 2010 were identified from the Hospital del Mar cancer registry (Barcelona, Spain) and followed up to 2016. The Hospital del Mar is a public university hospital in the city of Barcelona, which hosts 400 beds and provides coverage to a reference area of approximately 350,000 individuals.

Mode of detection

Detection mode was classified into screen-detected DCIS (women diagnosed through mammograms performed within the population-based BC screening program) and non-screen-detected DCIS (women with mammograms performed outside of the population-based screening program, such as opportunistic screening, presence of breast abnormalities/symptoms, and interval cancers). Interval cancers (n=3), defined as tumors arising after a negative screening episode and before the next screening invitation,

were analyzed within the non-screen-detected group. The Spanish Breast Cancer Screening Program is a population-based mammographic screening program that provides biennial mammography screening tests to women aged 50–69 years. It started gradually in 1990 and was implemented nationwide in 2005. Full coverage of the Hospital del Mar's area of influence was achieved in 1995. This program follows the European Guidelines for Quality Assurance in Mammographic Screening Recommendations and achieves the required standards.⁶

Within the non-screen-detected group, the presence of symptoms and past mammograms were not consistently registered or reported in charts. Women with screen-detected DCIS were 134 in total, while 77 were non-screen-detected. Both groups were diagnosed, treated, and followed up within the same BC unit at a reference hospital, following the same protocols for all patients.

Patient and tumor characteristics

Tumor and treatment variables were obtained from the hospital cancer registry. Additional clinical information was extracted through a retrospective clinical chart review. The "Shared clinical chart" (HC3) data source (storing all information on visits to publicly funded centers within Catalonia, Spain) was used to complete information on vital status, recurrences, readmissions, and complications.

Age at diagnosis and the presence of comorbidities were obtained through hospital records. The Charlson index was used to evaluate comorbidities. Radiologic mammography patterns were classified into presence or absence of calcifications. Pathology reports provided information on tumor focality (unifocal and multifocal), differentiation grade (I, II, and III), and tumor size (millimeter). Immunohistochemistry staining is routinely performed at our hospital. Following standard guidelines, positivity for ER, PR, and P53 requires more than 10% of cells testing positive. HER2 scores were determined through the HerceptTest kit. Hercept scores of 3 were considered positive, and scores of 0–1 were considered negative. Scores of 2 were considered positive when fluorescent in situ hybridization detected HER2/neu oncogene amplification. Molecular subtypes were constructed based on immunohistochemistry results, as proposed by Carey et al.⁷

Treatments

Type of surgery was classified as breast-conserving surgery (BCS, consisting of tumoral excision only) and mastectomy (complete removal of the breast and including radical or simple procedures). Surgical margins corresponded to the margin obtained at the final surgical procedure. Margins were considered free of disease when excisions maintained at least 2mm of distance to the

tumor. This criterion was evaluated retrospectively and based on current guidelines.⁸ Adjuvant radiotherapy and hormone therapy were also registered.

Follow-up information

Follow-up information was retrospectively reviewed from the hospital and HC3 charts to identify readmissions, complications, and BC recurrences. Trained staff (doctors) reviewed the clinical charts. Hospital readmissions included admissions within 3 months after surgery and had to be related to the disease. Readmissions were classified into re-excision, mastectomy, reconstruction, and others (which included unprogrammed causes for readmission such as infection and bleeding). Other complications were those developing 3 months after surgery until the end of follow-up and were classified as follows: surgery-related (seroma, recurrent skin infection, soft tissue necrosis, upper extremity paresthesia, upper extremity dysfunction, and lymphedema); persistent pain (when present for more than 3 months after surgery and occurring in relation to the surgical area, upper extremity, or chest); systemic complications (hypothyroidism, pneumonitis/pleural effusion, cardiac events, deep vein thrombosis, gynecologic events, cognitive dysfunction, osteoporosis, and weight gain); and psychological events (fatigue/anxiety/depression). On follow-up, each patient could present more than one type of complication.

BC recurrence required pathology confirmation, and all forms of BC recurrences (DCIS or invasive; local, regional, or distant) were considered. Disease-free survival was defined from the date of diagnosis to the date of BC recurrence or the date of the last follow-up. Median follow-up was 8.4 years (range: 0.4–16.5 years).

Statistical analyses

Women's tumor characteristics, treatment, and outcomes were compared according to detection mode. The chi-square or Fisher's exact tests were used where appropriate.

The impact of detection mode on BC recurrence, hospital readmission, and complications (total, surgical complications, pain, psychological events, and systemic complications) was estimated through multivariate logistic regression analysis. Different models were performed, one for each outcome, to obtain adjusted risks. Models were constructed following an explanatory modeling approach. For readmissions, Charlson score, type of surgery, age, and tumor size, adjusted the model. For complications, the model included Charlson score, type of surgery, hormone and radiotherapy, and age. The recurrence model was adjusted by age, tumor size type of surgery, hormone and radiotherapy, and presence of calcifications on mammography. All statistical testing

used a two-sided 0.05 level of significance. All analyses were performed with STATA/SE 13.1 (StataCorp LP, College Station, TX, USA).

Results

The study cohort included 211 women with DCIS BC. Patient and tumor characteristics by detection mode are shown in Table 1. The majority of women were screen-detected (63.5%). Regarding age, 50% of screen-detected patients were aged between 55–65 years. Among non-screen-detected, the majority (51.9%) were aged less than 55 years. A total of 67 (50.0%) women within the screen-detected group were initial screening participants, 58 (43.3%) successive screening participants, and 9 (6.7%) were successive screening participants who had missed a round. Compared to non-screen-detected DCIS, screen-detected DCIS more frequently presented with calcifications on mammography (57.9% versus 77.6%, $p=0.003$) and were smaller in size (57.5% < 20 mm versus 77.6%, $p=0.002$). No statistically significant differences in tumor grade or immunophenotype were noted by detection mode.

Regarding treatment characteristics, as shown in Table 2, the most common surgical procedure modality was BCS (86.3%). A higher proportion of women with non-screen-detected DCIS underwent mastectomy (20.8% versus 9.7%, $p=0.024$). Radiotherapy was more frequently used in women with screen-detected DCIS (85.61% versus 71.2%, $p=0.013$). Among the non-screen-detected group, 61 (79.2%) women were treated with BCS. Margin status was available for 59 women within this group, and a margin greater than 2 mm was attained in 44 (74.6%) patients. Radiotherapy was used among 52 (71%) women within this group (unknown in four patients). Free margin status was high, with more than 72% of the cohort attaining margins free of disease, and no differences were observed by detection mode.

In Table 3, differences in postoperative outcomes in screen and non-screen-detected DCIS are presented. A higher proportion of women with non-screen-detected DCIS experienced readmissions (28.6% versus 7.5, $p<0.0001$). Among this group, mastectomy was the most common procedure motivating readmission. Complications were higher within the non-screen-detected group. However, when complications were categorized, while proportions were higher within the non-screen-detected group, these differences were no longer statistically significant. The prevalence of psychological complications was almost 15% within the cohort, with a higher prevalence among women with non-screen-detected DCIS, although not statistically significant. Persistent pain was found to be 9.48% within the cohort. Regarding BC recurrence, 28 women experienced recurrences during the follow-up period (13.27%), 18 women in the screen-detected

Table 1. Comparison of baseline characteristics according to screening status.

	Overall	Detection mode		p-value
		Screen-detected	Non-screen-detected	
n (%)	211	134 (63.5)	77 (36.5)	
Patient characteristics				
Age				
<55	75	35 (26.1)	40 (51.9)	<0.001^a
55–65	72	67 (50.0)	5 (6.5)	
>65	64	32 (23.9)	32 (41.6)	
Charlson score				
0	139	91 (67.9)	48 (62.3)	0.465 ^b
1	45	27 (20.1)	18 (23.4)	
2	9	7 (5.2)	2 (2.6)	
≥3	18	9 (6.7)	9 (11.7)	
Tumor characteristics				
Calcifications				
No	62	30 (22.4)	32 (42.1)	0.003^a
Yes	148	104 (77.6)	44 (57.9)	
Unknown	1	0	1	
Tumor size				
≤20 mm	145	103 (78.0)	42 (57.5)	0.002^a
>20 mm	60	29 (22.0)	31 (42.5)	
Unknown	6	2	4	
Tumor focality				
Unifocal	167	109 (81.3)	58 (75.3)	0.300 ^a
Multifocal	44	25 (18.7)	19 (24.7)	
Differentiation grade				
Low	46	28 (21.7)	18 (25.4)	0.839 ^a
Intermediate	53	35 (27.1)	18 (25.4)	
High	101	66 (51.2)	35 (49.2)	
Unknown	11	5	6	
P53				
Positive	36	27 (20.7)	9 (12.2)	0.121 ^a
Negative	168	103 (79.3)	65 (87.8)	
Unknown	7	4	3	
Immunophenotype				
Luminal A	124	81 (61.8)	43 (58.9)	0.737 ^a
Luminal B	26	16 (12.2)	10 (13.7)	
Her2	37	25 (19.1)	12 (16.4)	
Triple negative	17	9 (6.9)	8 (11.0)	
Unknown	7	3	4	

Percentages calculated over the total without unknown values.

Statistically significant values are in bold ($p < 0.05$).

^aChi-square test.

^bFisher's exact test.

group (13.43%) and 10 (13%) in the non-screen-detected group ($p=0.927$).

Figure 1 plots the adjusted odds ratio (OR) of the association of mode of detection (non-screen-detected group) with recurrences, readmissions, and complications in women with DCIS. The risk of readmissions and overall complications was higher within the non-screen-detected group compared to screen-detected, as evidenced by an OR=6.25 (95% confidence interval (CI)=1.95–19.99) for

readmissions and an OR=2.41 (95% CI=1.95 - 4.86) for complications.

Discussion

While most of the discussion about BC screening programs focus on recurrences and survival, our data suggest that at the DCIS stage, other clinically relevant outcomes are affected by participation in screening programs. In this

Table 2. Treatment characteristics according to screening status.

	Overall	Detection mode		p-value
		Screen-detected	Non-screen-detected	
n (%)	211	134	77	
Procedure				
Mastectomy	29	13 (9.7)	16 (20.8)	0.024^a
BCS	182	121 (90.3)	61 (79.2)	
Radiotherapy				
No	40	19 (14.4)	21 (28.8)	0.013^a
Yes	165	113 (85.6)	52 (71.2)	
Unknown	6	2	4	
Hormone therapy				
No	101	59 (44.4)	42 (57.5)	0.070 ^a
Yes	105	74 (55.6)	31 (42.5)	
Unknown	5	1	4	
Margin status				
Affected (<2 mm)	44	29 (28.2)	15 (25.4)	0.707 ^a
Free (≥2 mm)	118	74 (71.8)	44 (74.6)	
Unknown	49	31	18	

BCS: breast-conserving surgery.

Percentages calculated over the total without unknown value. Mastectomy was considered as the definitive intervention.

Statistically significant values are in bold ($p < 0.05$).

^aChi-square test.

Table 3. Differences in postoperative outcomes according to screening status.

	Overall	Detection mode		p-value
		Screen-detected	Non-screen-detected	
n (%)	211	134	77	
Readmissions				
No	179 (84.83)	124 (92.54)	55 (71.43)	<0.0001^a
Yes	32 (15.17)	10 (7.46)	22 (28.57)	
Planned				
Re-excision				
Yes	10 (4.74)	5 (3.73)	5 (6.49)	0.502 ^b
Mastectomy				
Yes	11 (5.21)	2 (1.49)	9 (11.69)	0.002^b
Reconstruction				
Yes	5 (2.37)	1 (0.75)	4 (5.19)	0.061 ^b
Unplanned				
Yes	6 (2.84)	2 (1.49)	4 (7.79)	0.119 ^b
Complications				
No	104 (49.29)	73 (54.48)	31 (40.26)	
Yes	107 (50.71)	61 (45.52)	46 (59.74)	0.047^a
Surgical complications				
No	201 (95.26)	130 (97.01)	71 (92.21)	
Yes	10 (4.74)	4 (2.99)	6 (7.79)	0.175 ^b
Pain				
No	191 (90.52)	124 (92.54)	67 (87.01)	
Yes	20 (9.48)	10 (7.46)	10 (12.99)	0.187 ^a
Fatigue/anxiety/depression				
No	179 (84.83)	118 (88.06)	61 (79.22)	
Yes	32 (15.17)	16 (11.94)	16 (20.78)	0.085 ^a

(Continued)

Table 3. (Continued)

	Overall	Detection mode		p-value
		Screen-detected	Non-screen-detected	
Systemic/clinical events				
No	166 (78.67)	103 (76.87)	63 (81.82)	0.398 ^a
Yes	45 (21.13)	31 (23.13)	14 (18.18)	
Recurrences				
No	183 (86.73)	116 (86.57)	67 (87.01)	0.927 ^a
Yes	28 (13.27)	18 (13.43)	10 (12.99)	

Statistically significant values are in bold ($p < 0.05$).

^aChi-square test.

^bFisher's exact test.

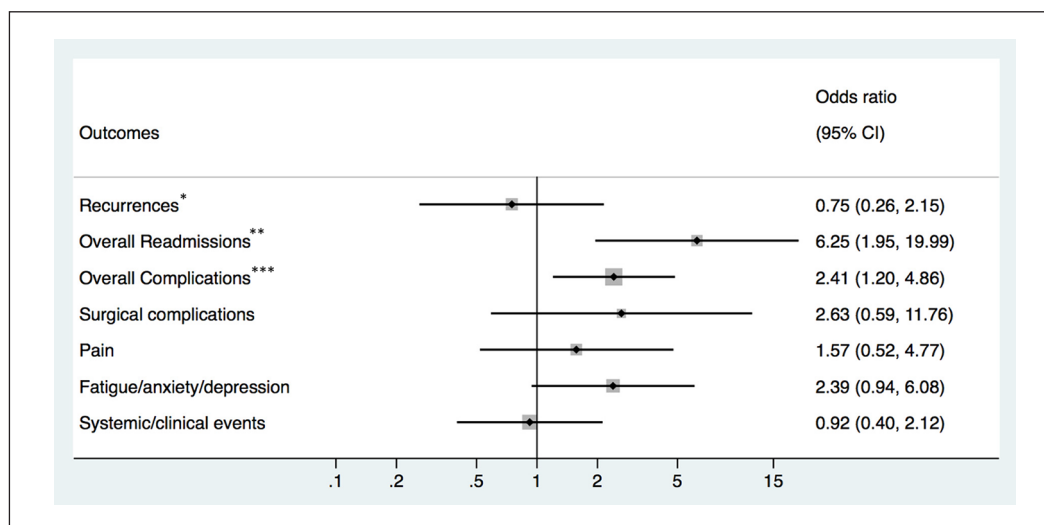


Figure 1. Adjusted OR for outcomes in women with non-screen-detected DCIS.

BCS: breast-conserving surgery.

Reference category is screen-detected breast DCIS.

*Final adjusted model: age, tumor size, calcification on mammography, type of surgery, and hormone and radiotherapy.

**Model adjusted by Charlson, type of surgery, age, and tumor size.

***Model adjusted by Charlson, type of surgery, hormone and radiotherapy, and age.

study, we have shown that women with screen-detected DCIS have a lower risk of readmissions and complications following treatment; and to our knowledge, this is the first study to examine these outcomes for DCIS BC.

Given the early detection of screen-detected DCIS, surgical treatment is less intense and lower complications and readmissions could be expected. However, after adjusting for potential confounders (age, comorbidities, treatment, and size), the association between readmission risk and detection mode was still present. Reconstruction or unplanned readmissions are expected following mastectomy or extensive surgeries. Mastectomy was significantly higher in the non-screen-detected group, compared to re-excision rates in which differences were non-significant. One hypothesis that could explain a higher mastectomy use among the non-screen-detected group is that younger patients may be overrepresented among this

group. In this sense, preoperative diagnosis may be difficult in younger women due to greater breast density and lower mammographic sensitivity leading to insufficient resections.⁹ Alvarado et al.¹⁰ described that adverse histological features may favor the use of mastectomy among this group; however, within our cohort, tumor characteristics did not differ significantly among age groups. Finally, we could not account for patient or surgeons' preferences regarding treatment choice.

Our observed reoperation rates are lower than what has been previously reported for DCIS.^{11,12} However, these rates are similar to what has been reported for invasive BC in Catalonia during a similar period.¹³

Complications were present in almost 50% of our cohort after more than 8 years of follow-up. Notably, complications were significantly higher in the non-screen-detected group and reached almost 60%. While

these numbers initially seemed high, this is the first study to analyze complications for DCIS broadly, so we relied on studies analyzing similar complications separately in BC survivors to support our findings. With regards to surgical complications and persistent pain, a systematic review performed by Verbelen et al.¹⁴ found that impairments with the highest prevalence after 2 years following sentinel lymph node-negative biopsy were pain (range: 5%–51%), numbness (range: 8%–51%), loss of strength (0%–35%), and decreased mobility (0%–38%). These values are notably higher than the prevalence we identified within our cohort for surgical and persistent pain complications combined. In line with our findings, the prevalence of persistent pain reported by Romero et al.⁵ was approximately 11% for BC survivors overall and 9% for DCIS. Surprisingly, despite the favorable prognosis for DCIS, fatigue, anxiety, and depression had a prevalence of 15% within our cohort. These results are similar to those reported in the previous studies.^{15,16} Interestingly, Gregorowitsch et al.¹⁷ have noted that severe depression is more common in DCIS than in early-stage invasive BC.

We observed a lower risk of complications in the screen-detected group. While we initially hypothesized that this could be mediated by treatment (lower mastectomies within this group), the association between detection method and complications persisted after adjusting for several covariates. Notably, only psychological complications (fatigue, anxiety, and depression) were borderline significant as a specific complication category in the non-screen-detected group. While our numbers are small, we hypothesize that different disease perceptions may occur in women according to detection mode. In this sense, it is known that exposure to unexpected stressors can have adverse psychological effects.¹⁸ Only a handful of studies have examined the effect of detection mode on distress levels in women with BC. Gibbons et al.¹⁹ compared stress anxiety and depression levels in women with BC according to detection mode. In their study, the prevalence of anxiety declined and neared 10% after 12 months following diagnosis, however, this decreasing trend was notably less pronounced within the screen-detected group, suggesting a slower adjustment process. These findings contrast with our results, in which prevalence was higher among the non-screen-detected group, but could be explained by differences in patient inclusion criteria (disease stage, length of follow-up, and the percentage of symptomatic women). However, another possibility is that these findings represent a self-selection bias, in which screening participants adopt an overall healthier lifestyle or adherence to treatments and recommendations.²⁰

Taken together, these findings highlight the need for specific interventions that can improve women's quality of life at the DCIS stage. While these findings can provide

information to aid informed decisions, it also highlights that a significant proportion of women experience pain and psychological distress. These areas could be improved with specific interventions. In terms of psychological distress, several studies have noted inaccurate risk perceptions among women with DCIS diagnosis, which affect their quality of life.^{21,22} In this sense, an appropriate transition of BC survivors to primary care could have an impact on disease risk and perception. For these reasons, we believe that readmissions and complications are relevant factors to consider when counseling women regarding screening participation, treatment decisions, or adjusting care in women with DCIS.

This study has some limitations. First, the sample size is small. However, in-depth information was available for each patient. Second, our study data were drawn from a single institution, limiting the generalizability of our results. However, treatment patterns within our institution are similar to those recently reported for Catalonia.²³ Regarding potential losses to follow-up, we used additional data sources (HC3) to minimize their impact. Relevant changes in DCIS diagnosis and treatment (such as mammogram equipment, margin free of disease width, biomarker testing, and treatment) have occurred over the study period (which includes cancers diagnosed between 2000 and 2010). However, analysis including a time-variable did not significantly modify the results (data not shown). Despite our intention to compare women with DCIS detected within the population-based screening program with those detected through mammograms not performed within the program, it is possible that opportunistic screening may have attenuated our results. Information regarding complications was extracted from a review of clinical charts and not by questionnaires. Consequently, these results may be underestimated. Nonetheless, we consider that these complications were significant enough to be documented in the medical records by the attending physicians. Furthermore, to our knowledge, this is the first study to analyze readmissions and complications in DCIS patients.

Conclusion

Our findings indicate that women with DCIS BC diagnosed through population-based BC screening program experience a lower risk of readmissions and complications than those diagnosed outside these programs. These findings can help aid women, and health professionals make informed decisions regarding the advantages of screening as well as to target specific interventions that improve women's disease knowledge and understanding.

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Author contributions

J.P., M.S., and X.C. designed the study; J.P. wrote the article, and M.S. and L.D. collaborated in drafting the article. J.P. performed the statistical analyses and M.S., L.D., M.V.-T., and M.R. contributed to the analyses and interpretation of results. J.P., L.D., and F.M. were involved in data acquisition. All authors revised the article critically for important intellectual content. All authors read and approved the final article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

All procedures reported in this study were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee of Parc de Salut Mar (CEIC-Parc de Salut MAR), Barcelona.

Informed consent

The study data were collected under a protocol approved by the ethics committee of Parc de Salut Mar (CEIC-Parc de Salut MAR), Barcelona.

ORCID iD

María Sala  <https://orcid.org/0000-0002-9955-8746>

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, M.S., on a reasonable request.

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