CLINICOPATHOLOGICAL CHARACTERISTICS OF BREAST CANCERS DIAGNOSED IN PARTICIPANTS, NON-PARTICIPANTS AND NOT INVITED TO THE BREAST CANCER SCREENING PROGRAMME IN NORTHERN PORTUGAL (2003-2008): PART ONE – EVALUATION.

CARACTERÍSTICAS CLINICOPATOLÓGICAS DOS CANCROS DA MAMA DIAGNOSTICADOS EM PARTICIPANTES, NÃO PARTICIPANTES E NÃO CONVIDADOS AO PROGRAMA DE RASTREIO DE CANCRO DA MAMA NO NORTE DE PORTUGAL EM (2003-2008): PARTE UM – AVALIAÇÃO

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ABSTRACT

The aim of this study was to evaluate the clinical and pathological characteristics of the invasive breast cancers diagnosed in women participant in the beginning of breast cancer screening programme, compared to cancers detected in non-participants and in not invited women. Data was retrieved from the population-based North Region Cancer Registry and from the organized population-based Breast Cancer Screening Programme (BCSP) of the north region of Portugal, and records were matched to select the three groups for comparison. In 125 screening participants, 75.8% of invasive breast cancers were ≤ 20 mm, 67.7% had no axillary lymph nodes metastasis and 58.1% were stage I. These characteristics were significantly more favourable than those found in breast cancers detected in non-participants (57 women) or not invited (314 women). After multivariable analysis, size remained the only distinguishing characteristic of breast cancers detected within the screening programme compared to the other two studied groups. Breast cancers detected in screening participants were significantly smaller, which is consistent with findings by other authors. The more favourable prognostic characteristics of the breast cancers detected in a population exposed to screening (including interval cancers) indicate a possible mortality reduction in the future.

Keywords: *Breast cancer; organized screening; non-participants; mammography.*

RESUMO

O objetivo deste estudo foi avaliar as características clínicas e patológicas dos cancros invasivos da mama, diagnosticados em mulheres participantes no programa de rastreio do cancro da mama, em comparação com os cancros detetados em não participantes e em mulheres não convidadas. Os dados foram obtidos do Registo Oncológico Regional do Norte, registo de base populacional, e do Programa de Rastreio de Cancro da Mama (PRCM), organizado, de base populacional da região norte de Portugal; foi avaliada a correspondência entre os dados para selecionar os três grupos para comparação. Em 125 participantes de rastreio, 75.8% dos cancros da mama invasivos eram ≤ 20 mm, 67.7% não tinham metástases nos gânglios linfáticos axilares e 58.1% eram estadio I. Estas características eram significativamente mais favoráveis do que as encontradas em cancros da mama detetados em não participantes (57 mulheres) ou não convidadas (314 mulheres). Após análise multivariável, o tamanho permaneceu a única característica distintiva dos cancros da mama detetados no âmbito do programa de rastreio em comparação com os outros dois grupos em estudo. Os cancros da mama detetados nas participantes do rastreio foram significativamente menores, o que é consistente com achados de outros autores. As características prognósticas mais favoráveis dos cancros da mama detetados numa população exposta ao rastreio (incluindo cancros de intervalo) indicam uma possível redução da mortalidade no futuro.

Palavras-chave: *Cancro da mama; Rastreio organizada; Não participantes; Mamografia.*

INTRODUCTION

High-quality population-based breast cancer screening programmes, with periodic mammographic examination of asymptomatic women became an important tool in cancer control (Dijck & Schouten, 2000; Lynge *et al.*, 2012). For logistic reasons the implementation of a new population-based screening programme in a certain country (or region) can take several years till it is fully implemented in all the geographical area considered; for that reason, during a certain time period, it happens that very similar neighbouring populations are being covered or not by the programme, creating an opportunity to compare likely outcomes between populations (Lynge *et al.*, 2012).

Comparisons of characteristics of the cancers diagnosed in women invited or not to an organized screening programme, and the analysis of differences between screened-detected and symptomatic breast cancers, have been used as a further approach in the evaluation of screening programmes (Shen *et al.*, 2005; Baré *et al.*, 2006; Bucchi *et al.*, 2008; Allgood *et al.*, 2011; Hofvind *et al.*, 2012; Nagtegaal & Duffy, 2013).

The organized population-based Breast Cancer Screening Programme (BCSP) implemented in the Northern Region of Portugal, conducted by the north branch of the Portuguese Cancer League (*Liga Portuguesa Contra o Cancro* – LPCC) started in 1999 in one municipality and gradually expanded its coverage in the north region (5 districts and 68 municipalities). In the period 2008/2009, a participation rate of 74.5% and coverage rate by invitation was 99.6% were achieved (Bento *et al.*, 2015). BCSP was implemented in the district of Bragança between 2003 and 2005 when full coverage was reached; in 2005, the estimated number of women aged 50-69 years living in the district was 19 554, representing 5.3% of the estimated 372 015 women of the same age living in the whole northern region. Bragança and Vila Real are neighbouring districts, with the same socioeconomical and cultural features and very close background breast cancer incidence (RORENO, 2002). In Vila Real the organized screening programme was only launched in 2009; in 2005, the estimated number of women aged 50-69 years living in this district was 27 644, representing 7.4% of the women of the same age group in the northern region.

We aimed at further contributing to the assessment of BCSP. For that purpose, the specific objective of this study was to compare the characteristics of the invasive breast cancers detected in populations with different screening exposure/participation status in our organized screening programme, regarding the beginning of the screening programme (part one).

METHODS

Briefly, the methods implemented at the BCSP were the following: every two years women aged between 45 and 69 years were sent a letter with an invitation for a two-view mammography examination at one of the mobile or fixed units. A blind-double reading was systematically performed at a dedicated centre by trained radiologists with a final reading by a third independent and experienced radiologist, in case of discrepancy. Since the beginning of the screening programme it has been operating in accordance with the European Guidelines (Perry *et al.*, 2006) and preliminary results have been published (Giordano *et al.*, 2012). A specific database with individual records for the screening procedures and results was created in 1999 (BCSP database).

Invasive breast cancers diagnosed in women resident in the northern region of Portugal have been registered since 1988, at the population-based North Region Cancer Registry (*Registo Oncológico Regional do Norte* – RORENO) which has high completeness (Castro *et al.*, 2012).

Data was retrieved from RORENO using the following criteria: invasive breast cancers diagnosed between 2003 and 2008, in women aged 50-69 years at diagnosis (to be in accordance with age group considered in the European Guidelines) (Perry *et al.*, 2006) and resident in the districts of Vila Real and Bragança. Then, information on the screening history of breast cancers in women resident in Bragança was retrieved from the BCSP database. Variables as name, date of birth and national health number were used for matching. Similar to the "screening exposure" (Baré *et al.*, 2006) and "participation" (Hofvind *et al.*, 2012) status classifications used by other authors, the above described information was used to select three groups for comparison:

- women invited and participating in the screening, including screen-detected cancers and interval cancers (residents in Bragança) named *participants* in this analysis;
- women invited but not participating in screening, including women who never attended organized screening procedures, and those whose last participation had been more than 2 years before (residents in Bragança), named *non-participants;*
- women not invited to screening, which includes two subgroups: those resident in Vila Real district, who were not invited to screening in the study period, and women resident in Bragança district with breast cancer diagnosed prior to an invitation to participate in the screening programme, named *not invited*.

Data collected from the BCSP and RORENO databases included the patient date of birth, date and round of last mammography, outcome of screening, screening exposure/participation status (participants, non-participants, not invited), municipality of residence, date of diagnosis of breast cancer, age at diagnosis, tumour size in mm (with further division in 3 groups, according to the cut-offs of the European Guidelines) (Perry *et al.*, 2006), histological type using the International Classification of Diseases for Oncology-3rd edition (8500, 8521 coded as ductal; 8520, 8522, 8524 coded as lobular; 8211, 8480, 8510, 8530, 8540 coded as other), histological grade according to Nottingham Grading System (Elston & Ellis, 1991), lymph node status, tumour stage (TNM classification – AJCC (Greene *et al.*, 2002)), first treatment (mastectomy, breast conserving surgery, chemotherapy). In cases with upfront chemotherapy, a clinical T and N were assigned. Information on biomarkers as oestrogen (ER) and progesterone (PR) receptors status, and detection of overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2) were registered according to the pathology reports.

Breast cancers detected in women participating in screening, in non-participants and in women not invited to screening were compared for each of the aforementioned variables. Comparisons were made pairwise. Proportions were compared using the Pearson χ^2 test or Fisher's exact test when χ^2 test

was not applicable, and one-way analysis of variance was used to compare the means of the continuous variables.

Unconditional multivariable logistic regression was used to assess the association between screening exposure/participation status and clinicopathological characteristics of breast cancer adjusted for possible confounder factors. Two models were tested for comparison of cancers detected in participants *versus* non-participants (including tumour size, lymph node status, grading, as covariates) and screening participants *versus* not invited (including tumour size, lymph node status, ER and PR expression, as covariates). Tumour size in the multivariable analysis was considered as ≤20 mm or > 20 mm. Since none of the screening participants had breast cancer with distant metastasis at diagnosis, this variable was not included in the multivariable models. HER2 was not used in this analysis, due to the small number of cases with this information. Differences were considered statistically significant for $P < 0.05$.

RESULTS

Between 2003 and 2008, 34476 exams were performed, with 125 breast cancer cases being detected in women participating in the programme (113 screen-detected and 12 interval cancers) and 57 breast cancers being diagnosed in non-participants, including 7 women with more than 2 years since last mammogram. In the same period, 314 cancers were detected in women not invited to screening, 278 were residents in Vila Real and 36 in Bragança.

The mean age of all (n= 496) selected women with breast cancer was 59.7±5.7 years, and there was no significant difference ($P = 0.56$) between the three groups. In table 1 are shown the main clinical and pathological characteristics of the three groups.

The predominant histological type was ductal and the proportions were very similar between groups.

In the group of screening participants, the proportion of cancers with maximum size ≤10 mm was 30.1%, < 15 mm was 52.1% and 75.8% were ≤ 20 mm. Compared to non-participants or not invited, screening participants had a significantly higher proportion of smaller breast tumours ($P < 0.001$ for the three cut-offs used).

When cancer dimensions were compared between non-participants and not invited groups, the proportion of breast cancers with a maximum dimension greater than 20 mm was significantly higher in the first group (66.7% compared to 49.5%, $P = 0.02$); when size cut-off values used were of 10 and 15 mm, no significant differences were observed. For all the other variables, there were no significant differences between these two groups (non-participants and not invited).

Cancers detected in participants were found to be better differentiated than those detected in non-participants ($P = 0.002$); compared to not invited group, participants had lower grade tumours, though significance ($P = 0.06$) was slightly above the classical significance level.

The tumours in screening participants had less frequently lymph node metastasis than non-participants or not invited groups ($P = 0.005$ and $P = 0.006$, respectively). None of the cancers in participants had distant metastasis at diagnosis and it was significantly different from the 4.2% of the cancers with distant metastasis detected among the not invited ($P = 0.02$). In non-participants, 1.9% (one case) had distant metastasis at diagnosis and it was not significantly different from the group of participants.

Cancers in participants were more frequently found in an earlier stage than in each of the other two groups, with 58.1% of the cancers detected in stage I among participants ($P < 0.001$ for both comparisons, table 1). At diagnosis, 22.2% and 37.5% of the breast cancers diagnosed in non-participants and in the not invited group, respectively, were classified as stage I.

Cancers in participants showed significantly higher proportion of ER and PR positivity than cancers in the not invited group ($P = 0.036$ and $P = 0.009$, respectively) but a similar proportion when compared with breast cancers of non-participants. Although in

Table 1 – **Distribution of clinicopathological characteristics of invasive breast cancers diagnosed in women participant, in non-participant and not invited to the organized population-based Breast Cancer Screening Programme in 2003-2008.**

Clinicopathological characteristics	Exposure/participation status			Significance level		
Variable value	Participants (P) n = 125 (%*)	Non-participants (NP) n = 57 (%*)	Not invited (NI) n = 314 (%*)	P value P/NP	P value P/NI	P value NP/NI
Histology						
Ductal	109 (87.2)	49 (86.0)	271 (86.3)	0.27	0.57	0.63
Lobular	13 (10.4)	4 (7.0)	29 (9.2)			
Other	3 (2.4)	4 (7.0)	14 (4.5)			
Tumour size						
↖10 mm	37 (30.1)	3 (5.6)	30 (11.2)	←0.001	←0.001	0.22
→10	86 (69.9)	51 (94.4)	239 (88.8)			
Missing	2	3	45			
Tumour size						
←15 mm	63 (52.1)	8 (19.0)	55 (24.2)	←0.001	←0.001	0.47
↗15 mm	58 (47.9)	34 (81.0)	172 (75.8)			
Missing	4	3	87			
Tumour size						
↖20 mm	94 (75.8)	18 (33.3)	142 (50.5)	←0.001	←0.001	0.02
→20 mm	30 (24.2)	36 (66.7)	139 (49.5)			
Missing	1	3	33			
Tumour grade						
Grade 1	27 (23.1)	8 (16.3)	48 (19.4)	0.002	0.06	0.15
Grade 2	75 (64.1)	23 (46.9)	141 (57.1)			
Grade 3	15 (12.8)	18 (36.7)	58 (23.5)			
Missing	8	8	67			
Lymph nodes						
negative	84 (67.7)	24 (45.3)	143 (53.0)	0.005	0.006	0.31
positive	40 (32.3)	29 (54.7)	127 (47.0)			
Missing	1	4	44			
Distant metastasis						
Negative	124 (100)	53 (98.1)	271 (95.8)	0.30	0.02	0.40
Positive	0 (0)	1 (1.9)	12 (4.2)			
Missing	1	3	31			
Stage						
I	72 (58.1)	12 (22.2)	106 (37.5)	←0.001	←0.001	0.11
II	40 (32.3)	23 (42.6)	94 (33.2)			
III	12 (9.7)	18 (33.3)	71 (25.1)			
IV	0	1 (1.9)	12 (4.2)			
Missing	1	3	31			
ER status						
Positive	108 (87.8)	43 (84.3)	206 (78.9)	0.54	0.036	0.38
Negative	15 (12.2)	8 (15.7)	55 (21.1)			
Missing	2	6	53			
PR status						
Positive	96 (78.0)	38 (74.5)	167 (64.7)	0.61	0.009	0.18
Negative	27 (22.0)	12 (25.5)	91 (35.3)			
Missing	2	6	56			
HER2 status						
Negative	56 (87.5)	25 (67.6)	126 (73.7)	0.015	0.024	0.25
Positive	8 (12.5)	12 (32.4)	45 (26.3)			
Missing	61	20	143			
Triple negative						
no	57 (89.1)	35 (94.6)	151 (88.3)	0.35	0.87	0.26
yes	7 (10.9)	2 (5.4)	20 (11.7)			
Missing	61	20	143			

* The percents were calculated excluding those cancers with value unknown; P/NP, screen participants compared to non-participants; P/NI, screen participants compared to not invited; NP/NI, non-participants compared to not invited; ER, oestrogen receptor; PR, progesterone receptor; HER2, epidermal growth factor receptor 2

Table 2 – **Multivariable logistic regression for the association between clinicopathological characteristics of breast cancer and mode of participation (non-participants or not invited *versus* screening participants).**

Parameters	OR adjusted for covariates	95% Confidence Interval	P value
Non participants/ Participants (n = 163)			
Tumour size			
↖20 mm	1		
→20 mm	4.36	2.00 – 9.71	←0.001
Lymph nodes			
negative	1		
positive	1.28	0.58 – 2.83	0.54
Tumour grade			
grade 1	1		
grade 2	0.78	0.28 – 2.19	0.64
grade 3	2.30	0.71 – 7.45	0.17
Not invited/ Participants (n = 370)			
Tumour size			
↖20 mm	1		
→20 mm	2.39	1.38 – 4.13	0.002
Lymph nodes			
negative	1		
positive	1.28	0.77 – 2.14	0.34
ER status			
Positive	1		
Negative	1.12	0.47 – 2.69	0.79
PR status			
Positive	1		
Negative	1.37	0.67 – 2.77	0.39

OR, odds ratio; ER, oestrogen receptor; PR, progesterone receptor

this last group cancers were slightly more positive for the hormonal receptors than in the not invited group, the difference was not significant ($P = 0.18$).

Information on HER2 status was missing for almost half of the cancers in participants and not invited women. The association between HER2 status and exposure/participation was statistically significant: negative status was more frequent in the participant group compared to non-participants or to not invited ($P = 0.015$ and $P = 0.024$, respectively). There were no significant differences according to exposure/participation status and the distribution of the triple-negative subtype.

In the multivariable analysis (table 2), 163 cases were included in the model for comparison of cancers in participants *versus* non-participants, and 370 cases for participants *versus* not invited group. Tumour size was the only significant variable in both final models. Larger tumours had higher probability to be found in cancers diagnosed in the group of non-participant ($P<0.001$) or not invited ($P=0.002$) groups compared to screening participants.

Information on treatment strategy was missing for 1.0% of participants, 12.3% of non-participants and 15.0% of not invited cases. When first treatment was surgery, the proportion of participants who underwent breast-conserving surgery was 57.4%, a value significantly higher compared to 34.1% of non-participants or 31.5% of not invited cancer cases ($P = 0.008$ and $P <0.001$, respectively). Chemotherapy as first treatment was recorded in 1.6% of participant women, which was significantly lower than 12.0%

among non-participants and 10.9% in the not invited group ($P = 0.003$ and $P = 0.002$, respectively).

DISCUSSION

In the evaluation of an organized screening programme, it is of paramount importance to describe the clinicopathological features of the cancers detected. In this study, we assessed these characteristics among breast cancers detected in a rolling population-based organized screening programme, comparing them to the breast cancers detected by usual practice or non-organized screening activities. Ideally, comparison of prognostic factors such as size and stage should be presented as rates instead of proportions. However, the phased implementation of screening programme in the geographical region considered in this study hindered an accurate assessment of the population at risk and precluded the calculation of rates.

The results should be interpreted within the limitations imposed by the design of the study, the small sample size of the groups and missing values. Due to the small number of cancers in the participant group, we were not able to differentiate initial from subsequent screening round, which prevented a more in-deep analysis on the effect of length bias and overdiagnosis (Hakama *et al.*, 1995). To allow for a higher pool of cases and, consequently, a more relevant statistical power in the analyses performed, we used the maximum number of years of operation of the screening programme. Also, some variables had a considerable amount of missing values. Clinical information for non-participants in the screening program (either not invited or invited but not participating) was only available through linkage with the population-based cancer registry, which has a passive notification of cases by hospital and private practitioners. On the other hand, information on screening participants is actively collected due to the quality evaluation of the screening programme.

In an initial analysis (univariate), breast cancers were significantly smaller among screened participants, less prone to the development of axillary metastasis and were found in an earlier stage, compared to breast cancers in women invited but not participant, or compared to the experience of breast cancer in a population not exposed to organized screening. Stage migration (down-staging) is an expected effect of screening (Hofvind *et al.*, 2012). This result is in agreement with other studies, either hospital-based or population-based, using comparison groups defined in a variety of ways, from cancers detected only by symptoms or opportunistic screening, cancers detected in populations not participating or not yet offered screening, among others (Bucchi *et al.*, 2005; Baré *et al.*, 2006; Burke *et al.*, 2008; Mook *et al.*, 2011; Hofvind *et al.*, 2012; Nagtegaal & Duffy, 2013). Nevertheless, after multivariable analysis, size remained the only distinguishing characteristic of breast cancers detected within the screening programme compared to the other two studied groups. The small numbers in the multivariable analysis possibly hampered the disclosure of other significant associations. It is recognized that that expected benefit of early detection of breast cancer is not determined solely by tumour size but other variables as nodal status and grade are also significant (Narod, 2012).

It was not surprising that conservative surgery was more frequently done in the screening participants, in which, detected cancers were smaller and with a higher proportion of stage I. Adoption of less harmful and more effective treatments in areas where organized screening has been implemented is a recognized benefit of screening programmes (Berry *et al.*, 2005; Bulliard *et al.*, 2009; Hofvind *et al.*, 2012; Segnan *et al.*, 2012).

Breast cancers detected in the not invited group had a significantly smaller dimension compared to cancers detected in women who didn´t participate or were less compliant with the organized screening programme. Several authors have raised this issue of the impact of opportunistic screening among populations without an organized screening service (Bulliard *et al.*, 2009; Welch, 2010; Hoff *et al.*, 2012;

Vanier *et al.*, 2013). Opportunistic screening exists in the Northern Region of Portugal, though we have no precise estimates of its magnitude; furthermore, we were not able to assign individually, the participation in opportunistic screening for this group of women as it is recommended (Bulliard *et al.*, 2009). Not forgetting these limitations, it is legitimate to argue that opportunistic screening should have a stronger impact in the not invited group, as this was the only possibility for earlier diagnosis in this population, and a likely explanation for the differences in tumour size reported in this study. Also, the implementation of a screening programme in a region has been considered to trigger cancer awareness in patients outside the screening programme, with a prognostic benefit in these (Kalager *et al.*, 2009; Mook *et al.*, 2011; Domingo *et al.*, 2013). The above explanations are plausible and eventually consistent with our findings and those published by other authors who reported a worse prognosis, as presenting larger dimensions for tumours detected in non-participants (Duffy *et al.*, 1991; McCann *et al.*, 1998; Stockton & McCann, 2001; Hofvind *et al.*, 2012).

The number of breast cancer cases with missing data on tumour size, nodal status and grading was greater in the not invited group than in the other two groups. However, it is unlikely that relevant selection bias had been introduced, since age and period of diagnosis (between 2003-2005 or 2006-2008) of the women with missing information did not differ from the age and period of diagnosis of the other women.

Reasons for non-participation can vary along the period of implementation of a screening programme (Mook *et al.*, 2011; Nagtegaal *et al.*, 2011). In the beginning, most of the women not participating were not invited, but afterwards non-participation happens for other reasons such as worse accessibility and lower socioeconomic status (Mook *et al.*, 2011; Hofvind *et al.*, 2012); this may lead to selection biases in this type of study (Mook *et al.*, 2011; Hoff *et al.*, 2012). We minimized the likelihood of this bias, since we were able to constitute more homogenous groups of not participant and non invited women to be compared.

Breast cancers detected in screening participants and non-participants or not invited women, were all diagnosed in the same time frame, close geographical location in the northern region and reflected the full experience of breast cancer incidence in the population. Thus, the possibility of bias due to improvement in cancer diagnosis and treatment in more recent years or bias due to selection of the cases was probably reduced.

Using the information from the organized population-based screening programme and matching it with information from a population-based cancer registry with high completeness, favours the validity of the reported associations. That is because it is more likely that we have got almost complete information on the clinicopathological characteristics of breast cancers in populations exposed and not exposed to an organized screening programme.

Breast cancers detected in screening participants were significantly smaller and tumour size is considered one of the strongest predictors of breast cancer behaviour (Day *et al.*, 1989). As stated by others, the more favourable prognostic characteristics of the breast cancers detected in a population exposed to screening (including interval cancers) indicate an eventual mortality reduction in the future, due to this cause (Hofvind *et al.*, 2008; Bulliard *et al.*, 2009; Hofvind *et al.*, 2012; Kim *et al.*, 2012). Thus, though this is a limited descriptive study, its findings are consistent with an effective screening programme, which will have to be confirmed in future assessments. Therefore, more recent data will be published in part two of BCSP evaluation.

DECLARATION OF CONFLICTING INTERESTS

Ana Aguiar was the Head of the Breast Cancer Screening Programme in the North Region of Portugal when the current study was performed. Vítor Veloso is the President of the Portuguese Cancer League, North Branch. For the remaining authors there are no conflicts of interest to disclose.

ETHICS

This study has been approved by the Ethics Committee of the Institution within the work was undertaken (reference CES.mr.229.2013) and it conforms to the provisions of the Declaration of Helsinki.

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Data de recepção do artigo:
23/02/2020

Data de aceitação do artigo:
26/06/2020