Original Research Article
Impact of Detection Mode in a Large Cohort of Women Taking Part in a Breast Screening Program

Running title: Impact of mode of detection in breast screenings

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Abstract:

Objective: The aim of this study is to evaluate the existing survival rate and clinical-pathological differences among patients with breast cancer detected by mammographic screening. **Materials and Methods:** Our multicenter cohort study examined 1248 patients who took part in a national screening program for the early detection of breast cancer for an eight-year period. **Results:** Of the two patient subgroups (interval and screening), we found significant differences in the distribution of prognostic factors, with interval cases presenting a lower mean age ($p=0.002$), higher percentages of HER2 or triple negative and lower percentages of luminal A or luminal B carcinomas ($p=0.001$), advanced stages ($p<0.001$), lower hormone receptor expression ($p<0.001$), poorer differentiation ($p<0.001$) and lower survival ($p<0.001$). Among the screening group, tumors detected during the first screening round presented a significant lower mean age ($p<0.001$), a lower frequency of comorbidities ($p=0.038$) and a tendency ($p<0.1$) to be diagnosed as triple negative breast carcinomas less frequently than incident cases. **Conclusion:** Our results point out that breast tumors detected during the first screening round are frequently characterized by a more benign phenotype than the rest of the screening subgroups, which could be of help when stratifying the risk of death and selecting the best treatment option for each patient.

Keywords: breast cancer, screening, survival, risk factors

Key points:

- Death risk may be overestimated in breast cancer patients diagnosed by screening programs when the method of detection is not considered.
- Breast cancer screening subgroups present survival and clinical-pathological differences.
- Patient risk stratification according to the screening subgroup to which they belong (prevalent, interval, incident) can help optimize their clinical management and treatment.

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Introduction

The World Health Organization (WHO) has declared cancer a leading cause of death worldwide, with an estimated 9.6 million deaths in 2018. Among the different cancer types, breast cancer caused 6.6% of worldwide cancer deaths in 2018, which represents the malignancy with higher incidence (24.2%, 32.825 new cases in Spain), mortality (15%) and 5-year prevalence (30.1%) rates among women worldwide [1].

According to the WHO, early detection is critical to improve breast cancer outcomes and survival. In this regard, despite selection, lead-time, length and overdiagnosis biases [2], the increasing implementation of screening programs has allowed for early patient diagnosis, quick treatment and an increased chance for successful treatment that can reduce up to 20% mortality rates [3]. For this reason, and despite reported handicaps of screening programs such as high costs or derived risks of ionizing radiation, breast self-examinations and other clinical explorations including mammography or ultrasonography represent the main tools for early diagnosis and timely treatment to lessen breast cancer morbidity. Indeed, although mammography screenings are not precise predictors of outcome [4] because of their inability to discriminate between malignant and benign breast masses, these programs along with histopathology studies have proven useful in significantly reducing mortality in women receiving adequate follow-up [5].

In some countries, breast cancer age-standardised mortality rates have decreased by 2-4% per year since the 1990s, but others have yet to achieve this outcome as countries with low breast cancer mortality rates are characterized by increased levels of essential health services coverage and higher numbers of public cancer centers[6] . There is evidence that two thirds of all women with breast cancer are still diagnosed after presenting to their clinicians with symptoms and not through screening [7].

Contrary to these symptomatic tumors usually characterized by a fast development, growth and spread, breast screenings normally detect a higher proportion of slow-growing tumors, that can even remain unnoticed in a woman's lifetime [4,8-10], which are associated with a better prognosis than tumors of similar size found outside patient screening [11-14]. In addition to differences in growth rate, the survival advantage of these cases may also be due to additional biological differences such as hormone receptors expression or HER2 (human epidermal growth factor receptor 2) status, among others [13,15,16]. Studies also show agreement that screening-detected breast cancers have relatively better tumor prognostic characteristics, biomarker profile and survival outcomes than those tumors diagnosed between two screenings [17,18], also known as interval tumors.

On the other hand, although the epidemiology, radiological and biological characteristics of interval breast cancers *versus* population mammography-detected screening tumors is well

documented [17,19,20], the prognostic and biological differences between screening-detected breast cancer subtypes, namely prevalent tumors, when diagnosed in the first screening round, or incident tumors when diagnosed in successive screening rounds, still need to be clarified. In this regard, a previous study of our research group reported significative differences between prevalent and incident tumors, showing that prevalent breast tumor cases present more favorable biologic and prognostic features than *incident cases* [21].

Despite the potential clinical benefit that these biological and clinical-pathological differences could have when selecting the most appropriate treatment and care methods for breast cancer patients, they are not contemplated in common Clinical Practice Guidelines. For this reason, and as a continuation of our previous investigations, in the present study we will evaluate if there are sociodemographic, clinical and biologic differences between prevalent, incident and interval breast cancer cases and their association with patient overall survival in a large cohort of healthy Spanish women participating in breast cancer screening programs.

Materials and Methods

Study design

We conducted an analytical study to evaluate the differences between breast cancer tumors detected during a screening test (prevalent and incident cases) and those detected in women after a negative screening test and before the next screening invitation (interval cases) (n=1086). We also evaluated the differences between prevalent and incident cases among screen-detected cases (n:741). In addition, we performed a survival study to evaluate the impact of the detection process (screen-detected cancer vs. interval breast cancer) on global survival.

Patients and samples

This observational study included 1086 women aged 45-69 years, with no known risk factors associated to breast cancer, who had participated in the screening program supported by four national breast-cancer screening programs which provide biannual mammograms and annual examinations for women with clinical indications of increased risk. This nationwide program meets the required standards [22]. The diagnoses and surgical interventions all took place during the period 2000-2008, with follow up until 2014

Variables

- Biologic characteristics: Phenotype (Luminal A, Luminal B, HER2, Triple Negative), Stage (*In situ*, Stage I, Stage II, Stage III), Estrogen Receptor Expression (Positive, Negative), Progesterone Receptor Expression (Positive, Negative), HER2 Receptor

enrichment (Positive, Negative), Ki67 score (<14%, >14%), Tumor Grade (Grade I, Grade II, Grade III), Death (Yes, No).

- Patient clinical history: Associated diseases required to calculate the Charlston Comorbidity Index (CCI): myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, connective tissue pathology, ulcerative disease, mild/moderate/severe hepatic disease, diabetes, diabetes with organic lesion, hemiplegia, renal pathology (moderate/severe), solid neoplasms, leukemia, malignant lymphoma, solid metastasis, and/or AIDS.
- Survival.
- Patient: age, family history.

Scope

Data were obtained from the multicenter retrospective cohort of women CAMISS (ClinicalTrials.gov Identifier NCT03165006) that included 1086 women with breast cancer participating in a population-based screening program in which three public hospitals, belonging to the Spanish National Health Service, in three Spanish regions (Andalusia, Canary Islands, Catalonia) were involved. The main objective of the CAMISS-Retrospective study was to evaluate the impact of the diagnosis process (screen-detected cancer vs. interval breast cancer) on overall survival [23].

Statistical analysis

Univariate analysis

Descriptive analysis segmented by the type of diagnosis (interval *versus* screening and prevalent *versus* incident). Comparison of the mean was performed by the Student's t-test after confirming the normal distribution of the quantitative variable and homogeneity of the variance, while comparison of frequencies was made by the chi-square test or by the Fisher's test when categories have expected frequencies less than 5 in more than 20% of cases.

Survival analysis

Survival analysis was performed using the Kaplan-Meier method to compare the types of diagnosis. In addition, Cox regression analysis was applied to estimate the risk of death and adjusted with entry criteria for the following variables: Age, Comorbidity (Presence, Absence), Tumor Stage (*In situ*, Stage I, Stage II, Stage III). The relative risk and the corresponding 95%

confidence interval were calculated. In the survival study, the primary endpoint was time elapsed to death from breast cancer from the time of diagnosis. Survival times for patients who were still alive were censored at the last date of follow-up. Patients who were still alive at the closing date were censored.

Results

We segmented and compared patient data for interval and screening breast cancer (incident and prevalent). The univariate analysis showed significant differences, with screening cases presenting higher mean age 58.8 (SD±5.5) than interval cases 57.7 (SD±5.3) ($p=0.002$) as well as higher frequency of hormone receptors expression ($p<0.001$) and luminal A and luminal B phenotypes ($p=0.001$). Screening tumors also presented a significantly different phenotype, with a lower frequency of triple negative tumors ($p=0.001$), less advanced stages ($p<0.001$) and lower grades ($p<0.001$) and deaths ($p<0.001$). We also found a tendency ($p<0.1$) for screening cases to have a family history of breast cancer more frequently than interval cases. We did not find any significant differences for comorbidity, Charlson Index, HER2 enrichment or Ki67 expression variables (Table 1).

The improved survival of screening cases is also evident in both the survival function (shown in Figure 1) and the multivariate Cox regression analysis, in which interval cases (Hazard Ratio HR: 1.63, Confidence Interval CI=1.13-2.36) ($p=0.01$) as well as the presence of comorbidity (HR: 1.48, CI=1.05-2.10) ($p=0.03$) and advanced stages (HR: 4.82, CI=1.17-19.80 for stage I; HR: 4.96, CI=1.19-20.62 for stage II and HR: 16.25, CI=3.89-67.77 for stage III) ($p<0.001$) are associated with an increased risk of death (Table 2).

We also found significant differences between prevalent and incident cases. In this case, patients with prevalent tumors presented a lower mean age ($p<0.001$), a lower frequency of comorbidity ($p=0.038$) and a tendency ($p=0.051$) to be diagnosed as triple negative less frequently. We did not find significative differences for the rest of the variables studied (Table 3).

The multivariate analysis showed an increased risk of death in advanced stages (HR: 3.88, CI=0.94-16.10 for stage I; HR: 3.26, CI=0.75-14.18 for stage II and HR: 15.69, CI=3.62-68.12 for stage III) ($p<0.001$) and, also revealed a similar behavior in survival numbers for both cancer subgroups (Table 4).

Discussion and conclusions

Our study of a large series of screening-detected breast carcinomas shows that not only variables which are generally associated with a less aggressive behavior and a better prognosis are more frequent in screening tumors rather than in interval tumors but also that, among screening tumors, prevalent cases exhibit the most favorable prognostic factors. Specifically, our study

shows the existence of a number of biological and clinical-pathological features among screening-detected breast tumors subtypes which reinforce the idea that the method of detection should be considered in risk estimations and avoid the use of aggressive treatments in those cases with a more favorable prognosis, such as breast cancer patients with prevalent tumors.

Consistent with other published studies reporting that the risk of distant metastases can be overestimated for breast cancer patients diagnosed by mammography screening unless the method of detection (mammography screening or other methods) is taken into account in the risk estimation [11], our results show that the method of detection can be considered as a prognostic factor of breast cancer patients even after adjusting for known tumor characteristics [12,24,25] possibly due to differences in tumor features and biology [13,20,26,27]. Specifically, we reveal that compared to interval tumors, screening-detected breast tumors present less aggressive biological characteristics and more favorable prognostic features such as low-grade, early-stage, expression of hormone receptors and Luminal A or Luminal B phenotypes, improved survival, lower mean age as well as a tendency to have cancer family history more frequently. Our results are in consonance with previous studies of our research group [28] which observed that screening cases show different biological characteristics that are generally associated with reduced tumor aggressiveness and enhanced survival such as positive expression of hormone receptors. Accordingly, interval cases are characterized by more-aggressive tumor characteristics and poorer survival outcomes [18,20,29] than screening-detected cases despite receiving more adjuvant chemotherapy [28,30].

Altogether, our results would support the need for cancer trialists to routinely collect information about method of detection when determining risk estimations [12] and the potential utility of considering the time of diagnosis within a breast screening program during decision-making on the best treatment strategy for the patient.

We also studied if there were any clinical or prognostic differences between prevalent and incident screening groups. We observed that prevalent tumors were characterized by some features, such as lower mean age, lower frequency of comorbidity and have a tendency to be diagnosed as triple negative less frequently (Table 2), generally associated with a better prognosis. Although a previous study of our group in a different cohort also found an association with an improved survival for prevalent screen-detected breast tumors [21], we did not find this survival advantage over incident tumors in this series, which would justify further studies with additional patient cohorts. Despite these contradictory results, considering that the prognosis of prevalent cases would not be affected by the use of adjuvant chemotherapy [28], tumor trialists should routinely collect information about method of detection [12], since the inclusion of the type of screening-detected breast cancer subgroup in clinical practice guidelines could help provide patients with the best care options.

Conclusions

Our results show that risk factors may be overestimated for breast cancer patients diagnosed by screening programs when the method of detection is not considered and also supports the need to continue investigating patient survival and clinical-pathological differences between breast tumors detected by screening, highlighting the potential benefit that patient risk stratification according to the screening subgroup to which they belong (prevalent, interval, incident) can have to optimize their clinical management and treatment.

Ethical statement

Our research comply with the guidelines for human studies and has been conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol has been reviewed and approved by the corresponding Scientific and Ethics Committee (003_nov_PR2-Diferencias Biológicas CA Mama).

Consent to participate statement: As the study only involved the collection of retrospective data, without modification, the informed consent of the individual subject was not required.

Conflicts of Interest:

The authors declare no conflict of interest.

Author Contributions

Conceptualization: MGA, XC, MS, MR; Methodology: IZ, TT, DP, FMC, KM, LD, MMV, MPR, ; Formal analysis and investigation: JL and FRR; Writing – original draft preparation: MGA, MR ; Writing – review and editing: MGA, MR and MS; Funding acquisition: MR ; Resources: ; Supervision: MR.

Data Availability Statement

Data underlying the findings are unsuitable for public deposits due to ethical grounds. However, they are available upon request to the corresponding author (MR).

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Table 1. Sociodemographic and clinical characteristics of patients with interval and screening breast cancer.

Variables	**Interval (n: 345)**		**Screening (n: 741)**		**p**
	n	**%**	**n**	**%**	
Age at diagnosis					
Mean – SD	*57.7*	*5.3*	*58.8*	*5.5*	0.002**
Comorbidity					
Absence	254	73.6	534	72.1	0.643
Presence	91	26.4	207	27.9	
Charlson Index					
Mean – SD	0.79	1.60	0.76	1.56	0.78
Family History[1]					
No	201	90.5	519	85.8	0.091
Yes	21	9.5	86	14.2	
Phenotype[2]					
Luminal A	140	45.9	278	56.9	0.001***
Luminal B	82	26.9	133	27.2	
Her2	33	10.8	38	7.8	
TNBC	50	16.4	40	8.2	
Stage[3]					
In situ	14	4.2	88	12.2	<0.001***
I	88	26.6	385	53.3	
II	144	43.5	199	27.5	
III	85	25.7	51	7.1	
Estrogen Receptors					
Negative	97	28.1	127	17.1	<0.001***
Positive	248	71.9	614	82.9	
Progesterone Receptors[4]					
Negative	147	42.7	233	31.5	<0.001***
Positive	197	57.3	507	68.5	
HER2[5]					
Negative	242	77.6	401	79.9	0.484
Positive	70	22.4	101	20.1	
Ki67 expression					
<14%	107	53.2	103	45	0.107
>14%	94	46.8	126	55	
Grade[7]					
I	51	17.9	183	31.1	<0.001***
II	107	37.5	252	42.9	
III	127	44.6	153	26	

Missing data: 1=259; 2=292; 3=32; 4=2; 5=272; 6=656; 7=213

TBNC: Triple Negative Breast Cancer

Table 2. Factors related to overall mortality by Cox regression analysis: screening and interval cases.

Risk factor	**p**	**HR**	**CI95%**	
			Lower	**Upper**
Type of diagnosis				
Screening		1,00		
Interval	0,01	1,63	1,13	2,36
Age				
	0,15	1,02	0,99	1,06
Comorbidity				
Absence		1,00		
Presence	0,03	1,48	1,05	2,10
Stage				
In situ		1,00		
I	<0,001	4,82	1,17	19,80
II		4,96	1,19	20,62
III		16,25	3,89	67,77

Table 3. Sociodemographic and clinical characteristics of patients with prevalent and incident breast cancer.

Variables	**Prevalent (n: 188)**		**Incident (n: 553)**		**p**
	n	%	n	%	
Age					
Mean – SD	*54.3*	*4.9*	*60,3*	*4.8*	<0.001***
Comorbidity					
Absence	147	78.2	387	70	0.038*
Presence	41	21.8	166	30	
Charlson Index					
Mean – SD	0.62	1.46	0,81	1.59	0.161
Family History[1]					
No	132	87.4	387	85.2	0.597
Yes	19	12.6	67	14.8	
Phenotype[2]					
Luminal A	60	60.0	218	56.0	0.051
Luminal B	27	27.0	106	27.2	
Her2	11	11.0	27	6.9	
TNBC	2	2.0	38	9.8	
Stage[3]					
In situ	26	14.4	62	11.4	0.725
I	92	50.8	293	54.1	
II	51	28.2	148	27.3	
III	12	6.6	39	7.2	
Estrogen Receptors					
Negative	32	17.0	95	17.2	1
Positive	156	83.0	458	82.8	
Progesterone Receptors[4]					
Negative	50	26.6	183	33.2	0.114
Positive	138	73.4	369	66.8	
HER2[5]					
Negative	78	77.2	323	80.5	0.545
Positive	23	22.8	78	19.5	
Ki67 expression					
<14%	28	48.3	75	43.9	0.666
>14%	30	51.7	96	56.1	
Grade[7]					
I	48	34.8	135	30.0	0.199
II	62	44.9	190	42.2	
III	28	20.3	125	27.8	

Missing data: 1=259 ; 2=292; 3=32; 4=2; 5=272; 6=656; 7=213
TBNC: Triple Negative Breast Cancer

Table 4. Factors related to overall mortality by Cox regression analysis: prevalent and incident cases.

Risk factor	**β**	**P**	**HR**	**CI95%**	
				Lower	**Upper**
Type of diagnosis					
Prevalent			1,00		
Incident	0,01	0,98	1,01	0,56	1,81
Age	0,04	0,10	1,04	0,99	1,09
Comorbidity					
Absence			1,00		
Presence	0,18	0,46	1,20	0,73	1,97
Stage					
In situ			1,00		
I	1,36	<0,001	3,88	0,94	16,10
II	1,18		3,26	0,75	14,18
III	2,75		15,69	3,62	68,12