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Clinical and radiological features of breast tumors according to history of false-positive results in mammography screening

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ABSTRACT

Background: Women with a false-positive result after a screening mammogram have an increased risk of cancer detection in subsequent participations, especially after assessments involving cytology or biopsy. We aimed to compare women's personal characteristics, tumoral features and the radiological appearance of cancers with and without a previous false-positive result generated by additional imaging or invasive procedures.

Methods: From 1996 to 2007, 111,098 women aged 45–69 years participated in four population-based breast cancer screening programs in Spain, and 1281 cancers were detected. We included all cancers detected in subsequent screenings ($n = 703$) and explored the occurrence of previous false-positive results. We identified false-positives requiring additional imaging or invasive procedures. Differences on tumoral features (invasiveness, tumor size, and lymph node status) and radiological appearance were assessed by Chi-square test, and agreement between the location of cancer and prior suspicious by Cohen's kappa coefficient. A multivariate analysis was preformed to evaluate the effect of previous screening results and age on the odds of presenting an in situ carcinoma.

Results: Among the 703 cancers detected in subsequent screenings, 148 women (21.1%) had a previous false-positive result. Of these, 105 were by additional imaging and 43 by invasive procedures. Women with prior false-positive result requiring invasive assessment, compared to women with negative tests, and women with prior false-positive requiring additional imaging, had a higher proportion of in situ carcinomas (31.7%, 15.3%, 12.9%, respectively; $p = 0.014$) and microcalcifications (37.2%, 20.2%, 9.5%, respectively; $p = 0.003$). The proportion of in situ carcinomas was even higher in women over 60 years (39.2%, 12.5%, 13.0%, respectively; $p = 0.001$). Ipsilateral cancer was observed in 65.7% of cases with prior cytology or biopsy ($k = 0.479$; 95%CI: 0.330–0.794).

Conclusion: A large number of in situ malignancies and calcification patterns were found among women with prior false-positive result in mammography screening requiring cytology or biopsies, suggesting progression from a previously benign lesion.

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1. Introduction

In breast cancer screening programs, most women with a screen-detected abnormality will not be diagnosed with cancer after being recalled for further assessment [1]. This further assessment may imply additional imaging tests or invasive procedures, which will usually rule out a malignancy and will therefore generate a false-positive result. However, women with false-positive results have been reported to be at higher risk for cancer detection in subsequent screening rounds [2–5]. Although this association seems consistent from a statistical point of view, a clear explanation is lacking and few studies have specifically evaluated this relationship.

The high risk of breast cancer after a false-positive result may be partly explained by the false-negative hypothesis (that is, cancers missed after further assessments in the screening that are diagnosed at the next screening) [6]. Another explanation is that women with benign breast disease have a greater risk of developing invasive breast carcinoma [7,8]. Specific information on imaging and pathological features might help to improve understanding of this event. Nonetheless, to date, few studies have evaluated information on tumoral characteristics, radiological appearance, and the location of the two lesions [4,9,10], and none have distinguished between a false-positive involving invasive procedures or just additional imaging.

This study aimed to compare women's personal characteristics, tumoral features and their radiological appearance among patients with and without a previous false-positive result generated by additional imaging or invasive procedures, and to assess the agreement between the location of the false-positive lesion and that of the subsequent malignant tumor.

2. Materials and methods

2.1. Settings

Data were obtained from five radiology units from four different population-based breast cancer screening programs in Spain (Cantabria, Barcelona, Girona and Valencia) between 1996 and 2007. More detailed information on screening in the programs involved in the study and on database construction has been previously reported [11]. Briefly, women in the target population, aged between 45 and 69 years, receive information on screening and are invited to undergo mammography at 2-yearly intervals. All programs are based on the European guidelines for quality assurance in screening mammography, and their results meet the required standard [12,13]. Since 2007, the programs have obtained two views (mediolateral oblique and craniocaudal). Previously, a single view was obtained for subsequent screenings in one program. Reading methods were single reading in one program, double reading with consensus in two programs, and double reading with arbitration in one program. All radiology units began their screening activities between 1996 and 1998 using screen-film radiographic technology and switched to full-field digital mammography between September 2004 and January 2005.

This study was approved by the Ethics Committee of our institution. Informed consent was not required.

2.2. Study population

Women participating in at least two screening rounds (thus having the chance of a false-positive result) and diagnosed with cancer in the screening process were included in this study. Of 291,218 mammograms performed during the study period, 1281 cancers were detected. Of these 1281 cancers, 578 were detected at the first screening and were therefore excluded from the analysis. A total of 703 women with cancer were included in the analysis. These women had a median of three screening participations (interquartile range (IQR): 2–4). Interval cancers – i.e. cancers manifesting clinically between two screening mammograms – were not included in the study.

2.3. Screening results: definition of a false positive results and cancer diagnosis

Within the screening program, women with a negative mammographic reading (equivalent to BI-RADS score of 1 and 2) are recalled for a new screening mammogram at 24 months. Women with a positive mammographic reading (equivalent to a BI-RADS score of 3, 4, 5 and 0) are immediately recalled for further assessments to exclude malignancy within the screening program. The diagnostic work-up for additional evaluation takes place within a maximum of 2 months after screening.

A positive result in the screening test was considered a false-positive result if, after immediate further assessments – which can include invasive or non-invasive procedures – cancer was not diagnosed. Non-invasive procedures may include additional mammography, magnetic resonance imaging, or ultrasonography; invasive procedures encompass fine-needle aspiration cytology, core-biopsy, or open biopsy. A definitive diagnosis of breast cancer was always histopathologically confirmed. If cancer is ruled out after the additional evaluation, women are routinely invited to participate again 24 months after the initial screening test.

2.4. Study variables

Women's personal characteristics (age, familial history of malignant breast disease, or menopausal status) were collected at each woman's attendance through a questionnaire. Tumor-related characteristics (invasiveness, size, lymph node status) were identified from screening databases.

Information on location and radiological patterns was collected for both the false-positive episode and the cancer diagnosis from the radiological reports. There were three possible locations: left breast, right breast or both breasts. Radiological patterns were classified into masses, distortions, calcifications, asymmetries, and multiple patterns.

2.5. Statistical analysis

Women were classified according to whether they had a false-positive result or not. Among women with a previous false-positive result, we differentiated between those that involved a non-invasive or an invasive procedure. We calculated Pearson's χ^2 test to compare women's personal characteristics and tumoral features between study groups. An analysis stratified by age was performed to assess the percentage of in situ carcinomas among study groups. For the purpose of this subanalysis, age was collapsed into two categories: <60 years old, and ≥ 60 years old. A logistic regression analysis was performed to examine the association between previous screening results on the odds of presenting an in situ carcinoma, adjusting by age. The potential interaction between age and screening results was tested in the logistic regression model. The interaction term was not statistically significant.

We conducted a sensitivity analysis to evaluate the inclusion of false-positive results in the previous screening round or in two or more screening rounds before the cancer diagnosis. The analysis confirmed equivalent results regarding women's personal characteristics and tumoral features. Consequently, in the above-mentioned analyses we included any false-positive result reported before the cancer diagnosis to enhance the study power.