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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.

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 ith screening, and is 0 otherwise. The coefficients of the time indicators are expressed by α_i and are the intercepts in the model (multiple intercept model). As in any other regression model X_j is the jth study factor (i.e. first-degree familial history of breast cancer, attended previous screening invitation, etc.), and β_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