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Increased risk of breast cancer in women with false-positive test: The role of misclassification

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ABSTRACT

Introduction: Studies have shown that women with a false-positive result from mammography screening have an excess risk for breast cancer compared with women who only have negative results. We aimed to assess the excess risk of cancer after a false-positive result excluding cases of misclassification, i.e. women who were actually false-negatives instead of false-positives.
Method: We used data from the Copenhagen Mammography Screening Programme, Denmark. The study population was the 295 women, out of 4743 recalled women from a total of 58,003 participants, with a false-positive test during the screening period 1991–2005 and who later developed breast cancer. Cancers that developed in the same location as the finding that initially caused the recall was studied in-depth in order to establish whether there had been misclassification.
Results: Seventy-two cases were found to be misclassified. When the women with misclassified tests had been excluded, there was an excess risk of breast cancer of 27% (RR = 1.27, 95% confidence interval (CI), 1.11–1.46) among the women with a false-positive test compared to women with only negative tests. Women with a false-positive test determined at assessment had an excess risk of 27%, while false-positives determined at surgery had an excess risk of 30%.
Conclusions: The results indicate that the increased risk is not explained only by misclassification. The excess risk remains for false-positives determined at assessment as well as at surgery, which favours some biological susceptibility. Further research into the true excess risk of false positives is warranted.

1. Introduction

Breast cancer is the most common cancer in women [1]. Screening for breast cancer with mammography has proven to lower the mortality from breast cancer in the population [2–5]. However, with screening also follows some disadvantages such as false-positive tests. A false-positive test refers to women who are recalled for further assessment after a screening mammogram, and then found to be free of breast cancer. The risk of getting a false-positive test varies greatly between screening programmes, so while the estimated risk over 10 screens in the US varies between 58% and 77%, with an estimate of 63% as the most reasonable assumption [6] the corresponding percentage for the here studied programme in Copenhagen, Denmark is close to 16% [7].

In a recently published study [8], women with false-positive test were found to have an increased risk of breast cancer later in life, compared to women with only negative tests. The increased risk remained up to 12 years or more after the first false-positive test, but was somewhat reduced for screening in later time periods, possibly due to enhanced test quality e.g. improved imaging techniques, more experienced radiologists, etc. This excess risk of breast cancer may be due to misclassification of disease status, meaning that women with an abnormal mammogram were falsely declared negative, when they should actually having been declared as having cancer, similar to a study by Peeters et al. [9]. Another possible explanation could be that these women have some biological susceptibility for increased risk of breast cancer, such as benign breast disease [10–17]. What favours the hypothesis of misclassification is the more than doubled risk at the first screen following the false-positive test and that the excess risk was higher in the early technology phase (screened from January 1, 1994 to December 31, 1998 and followed up to December 31, 2000) than in the late technology phase (screened from January 1, 2001 to December 31, 2005 and followed up to December 31, 2007). On the

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other hand, excess breast cancer risk for up to 12 years and more after the first false-positive test favours the hypothesis of biological susceptibility.

To assess the excess risk of breast cancer in women who have had a false-positive test at screening excluding misclassification we re-analysed the data, calculating risk of breast cancer excluding the women with cancer in the same location as the finding causing the original recall, as well as studying the role of breast density and cancer morphology in misclassification. To our knowledge this has not been done before.

2. Method and materials

We used data from a population-based screening mammography programme in Copenhagen, Denmark. Screening took place between 1991 and 2005. A total of 58,003 women were included in the analysis out of which 4743 were recalled and subsequently declared negative, i.e. women with a false-positive result. We studied the 295 women with a false-positive test during the screening period and who later developed breast cancer (274 with invasive breast cancer and 21 with ductal carcinoma in situ (DCIS)) within the follow-up until April 17, 2008.

Population-based screening mammography started in Copenhagen, Denmark, in April 1991 and is organised in approximately biennial invitation rounds. During our study period all women aged 50–69 years were, in each invitation round, personally invited to screening. Screen-film mammography was used throughout the study period, and mammograms were evaluated independently by two radiologists. Women with suspicious findings were recalled for assessment using the triple test consisting of clinical examination, mammography, and needle biopsy. From 1992 onwards, for palpable and/or mammographically uncertain, suspicious, or malignant lesions, mammography was supplemented with whole breast ultrasound examination, as well as ultrasound guided fine needle aspiration cytology and/or histological biopsies. High frequency ultrasound devices were introduced in 2001, and since 2002 stereotactic biopsy equipment were used for suspicious micro-calcifications and impalpable mammographic findings that could not be found by ultrasound. In the event of inconsistent findings in the triple test, further investigations were undertaken. If consensus still could not be reached, the women were referred to surgical biopsy. False-positive tests were defined as Type 1, when the test was determined negative at assessment and as Type 2 when the test was determined negative at surgery.

To determine whether there had been a misclassification a radiologist (MK) compared the initial test results that gave the reason for recall with the later cancer location. Cancers that developed in the same quadrant as the finding that initially caused the recall was studied in-depth in order to establish whether there had been misclassification or not. For each patient the initial screen was compared with the diagnostic screens and cancer was verified by use of the Danish Pathology Register. For any uncertain cases a second radiologist (IV) was called in. If certainty could not be reached, the case was not defined as misclassified.

2.1. Data analysis

Data from the mammography register was linked to data from the Cancer Registry and the Danish Pathology Register by means of the unique Danish Civil Registration System (CRS) Number. The study included breast cancer (C50), and carcinoma in situ (D05) according to the International Classification of Disease no. 10 (ICD-10). The incidence rate of breast cancer was analysed as a log-linear function of attained age (a) and exposure status (s) and expressed as $\ln(\lambda_{as}) = \alpha + \beta_a a + \beta_s s$, where α is the intercept and β is the slope of the regression line. Age was divided into 5-year age-groups (50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and 85–89 years) and exposure status was divided into false-positive or never false-positive (hereafter called "negative"). Person years at risk were calculated from date of first screen until censoring or end of follow-up. Women contributed person years at risk to the negative group as long as the screening tests were negative only. Women contributed person years at risk to the false-positive group from the date of the first false-positive test. Women were censored at death, breast cancer diagnosis, emigration, or end of follow-up on April 17, 2008, whichever came first. A full description of the methodology has been reported elsewhere [8].

In the further analysis of the excess risk the cases determined as misclassified were excluded from the calculations of incidence rate.

Mammographic density was evaluated for the 295 false-positives with cancer by a radiologist (MK) according to standard methods and in accordance with the Breast Imaging Reporting and Data System (BIRADS). In the analysis BIRADS-1 (indicating a predominantly fatty breast) and BIRADS-2 (indicating scattered fibroglandular densities) were grouped under 'low mammographic density', while BIRADS-3 (indicating a breast that is heterogeneously dense) and BIRADS-4, (indicating an extremely dense breast) were grouped under 'high mammographic density'. For 13 cases (4.4%) BIRADS could not be established. The statistical calculations were done using SAS version 9.1 (SAS Institute Inc., Cary, NC).

The Chi-square test was used to compare differences in tumour size, receptor, and nodal status between the breast cancers diagnosed in the groups of misclassified and non-misclassified. Data were supplied by the Danish Breast Cancer Cooperative Group (DBCG).

3. Results

A total of 58,003 women were included in the analysis out of which 4743 were recalled. Out of the 295 that later got breast cancer, 72 cases were found to be misclassified, which represents a false-negative rate of 1.5% (72/4743 recalled women) in women recalled for assessment. The excess risk was reduced after excluding the misclassified, but there was still a significant excess risk of breast cancer of 27% (RR = 1.27, 95% CI, 1.11–1.46) among the women with a false-positive test compared to women with only negative tests. Women with a false-positive test determined at assessment (Type 1) had an excess risk of 27% (RR = 1.27, 95% CI, 1.09–1.46), while false-positives determined at surgery (Type 2) had an excess risk of 30% (RR = 1.30, 95% CI, 0.86–1.96), Table 1.

Table 1
Relative risk of breast cancer for women with and without non-misclassified false-positive screening tests versus women with negative screening tests (invasive and DCIS).

Cohort	Person years at risk	Breast cancer Total number	Relative risk, age adjusted (95% CI)
Negative test	580,450	1969	1.0 Ref
False positive, including misclassifications	50,589	295	1.67 (1.45–1.88)
Negative test	580,450	1969	1.0 Ref
False positive, excluding misclassifications	50,304	223	1.27 (1.11–1.46)
Type 1 FP excl MC	45,282	200	1.27 (1.09–1.46)
Type 2 FP excl MC	5022	23	1.30 (0.86–1.96)

Note: Type 1 FP, established as false-positive after assessment; Type 2 FP, established as false-positive after surgery; MC, misclassifications.