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Interval breast cancers: Absolute and proportional incidence and blinded review in a community mammographic screening program

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ABSTRACT

Purpose: To evaluate the performance of the first years since the beginning of a mammographic population-based screening program.
Materials and methods: Women aged 49–69 were invited biennially for two-view film-screen mammography and double reading without arbitration was performed. Interval cancers (ICs) from 2001 to 2006 were identified using screening archives, local pathology archives, and hospital discharge records. The proportional incidence of IC was determined considering breast cancers expected without screening. Three offsite radiologists experienced in breast cancer screening blindly evaluated mammograms prior to diagnosis, randomly mixed with negative mammograms (1:2 ratio). Cases unrecalled at review were considered as true ICs, those recalled by only one reviewer as minimal signs, and those recalled by two or three reviewers as missed cancers. T and N stage of the reviewed ICs were evaluated and compared.
Results: A total of 86,276 first level mammograms were performed. Mean recall rate was 6.8% at first and 4.6% at repeat screening. We had 476 screen-detected cancers and 145 ICs (10 of them ductal carcinomas in situ). Absolute incidence was 17 per 10,000 screening examinations. Invasive proportional incidence was 19% (44/234) in the first year, 39% (91/234) in the second year, and 29% (135/468) in the two-year interval. Of 145 ICs, 130 (90%) were reviewed mixed with 287 negative controls: 55% (71/130) resulted to be true ICs, 24% (31/130) minimal signs, and 22% (28/130) missed cancers. The rate of ICs diagnosed in the first year interval was 21% (15/71) for true ICs, 46% (13/28) for missed cancers, and 39% (12/31) for minimal signs, with a significant difference of true ICs rate compared to missed cancers rate ($p = 0.012$). A higher rate of T3 and T4 stages was found for missed cancers (18%, 5/28) compared to minimal signs (6%, 2/31) or true ICs (8%, 6/71), while the rate of N2 and N3 stage for both minimal signs (19%, 6/31) or missed cancers (25%, 7/28) was higher than that for true ICs (10%, 7/71), although all these differences were not significant ($p \geq 0.480$).
Conclusion: These results showed the possibility to comply with European Community standards in the first years of a screening program implementation.

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1. Introduction

The European Union [1] and the Italian Ministry of Health [2] recommend the use of a number indirect indicators to evaluate the effectiveness of population-based mammographic screening programs. Three of these indicators derive from the analysis of interval cancers (ICs) and allow for an early evaluation of the program performance. These indicators are: (a) IC absolute incidence (the rate between observed ICs and number of screening examinations); (b) IC proportional incidence (the rate between observed ICs and cancers expected in the absence of a screening program, the latter being the breast cancer incidence); and (c) blinded review of false negative screening mammograms prior ICs, classified according to well defined categories [3].

The purpose of this paper is to present the analysis of the absolute and proportional incidences of IC and the results of a blinded review of ICs observed at a population-based biannual mammographic screening program between 2001 and 2006.

2. Materials and methods

Institutional Review board approval was not needed in this kind of study. In 2001, a mammographic screening program was activated in the territory of Azienda Sanitaria Locale Milano 2 (Italy), involving six centers. The local department of preventive medicine of our district sent mail letters to women living in the area aged from 49 to 69, registered to the regional health system registry.

Each mammogram of the program was independently read by two radiologists according the double blind reading procedure, without arbitrate [4]. The large majority of radiologists had no previous direct experience in organized screening but had previous experience in diagnostic mammography for symptomatic women and in mammography for asymptomatic women (spontaneous screening). For each woman, standard two-view (cranio-caudal and medio-lateral oblique projections) film-screen mammography was performed as initial screening. Repeat standard views, spot-view with or without magnification, dedicated views, focused high-frequency ultrasound, core-needle biopsy or vacuum-assisted biopsy under ultrasound or mammographic stereotactic guidance were performed as standard clinical workup if any suspicious image was found at least by one radiologist; breast MR examination or excisional biopsy were performed only if needed according a multidisciplinary assessment.

From 2001 to 2006, 86,276 women accepted the invitation and entered the screening program. The crude attendance rate – i.e., the number of women who performed mammography through the organized screening program of all the invited women – was 48% (86,276/179,742). The adjusted attendance rate – i.e., the crude attendance rate corrected adding women who refused to perform mammography through the organized screening program because they already performed opportunistic mammography recently – was 58% (103,711/179,742). We had 476 newly diagnosed screen-detected breast cancer, 13% (60/476) being ductal carcinoma in situ (DCIS) and 67% (321/476) being T1-stage invasive carcinoma [5]. The recall rate was 6.8% at first screening and 4.6% at repeat screening [5], in agreement with international [1] and national guidelines [6]. Overall cancer detection rate was 5.5‰, 6.5‰ at first screening and 4.5‰ at repeat screening [5].

Interval cancers were identified by linking our screening program database with those of the local pathology archives and with hospital discharge records provided by local health authorities. We considered all proven invasive breast cancers and DCIS diagnosed after a negative screening mammogram (or after a positive first level mammogram with further negative examination). At the time of the analysis, follow-up data were available up to December 2008, thus all ICs with negative screening mammogram performed between January 2001 and December 2006 were considered in the present paper. The number of expected cancers was obtained by multiplying the number of patients in each age group (50–54, 55–59, 60–64, 65–69) of our screening program by the age-specific breast cancer incidence provided by the local cancer registry of the near city of Varese (Italy), with the same population characteristics of our territory, referred to a time period preceding the beginning of our screening program.

The absolute and proportional incidence of ICs were calculated, the latter as the ratio between observed ICs (identified according to the abovementioned process) and expected cancers. Although European guidelines [1] consider both invasive cancers and DCIS as ICs, we used only invasive cancers to calculate proportional incidence. This was done because the estimate of expected cancers was based on cancer incidence provided by the local cancer registry, which takes into account invasive cancers only. We stratified ICs distribution according to the interval year of diagnosis (first or second) and correlated these data with T and N stage parameters.

Blinded reading review was performed by mixing previous screening film mammograms of women diagnosed with ICs and negative mammograms (i.e., mammograms of women with the same age and breast density performed between 2001 and 2006 with a negative mammographic follow-up of at least 2 years) with a ratio 1:2. Three offsite radiologists with different screening mammography experience (with 30, 15, and 3 years and at least 5000 mammograms read per year) blindly and randomly evaluated the pool of mixed bilateral mammograms and marked on a paper scheme of the four mammographic views the site of the finding considered worth of further assessment. The correspondence between the finding indicated by each reviewer and the real site of IC occurrence was verified. The type of mammographic abnormality and the mammographic density were not reported. Unrecalled cases at blinded review were considered as true ICs, cases recalled by only one reviewer as minimal signs, cases recalled by two or three reviewers as missed cancers.

IC proportional incidence and missed cancers rate at review were calculated and compared with European recommended standards [1]. Cancer probability in blinded reading was obtained dividing ICs by the total of ICs and negative controls recalled by one, two, or three reviewers. An analysis of the distribution between first and second year diagnosed ICs and the respective correlation with T and N stage was performed for all the reviewed ICs. The same analysis was performed stratifying ICs for two age groups (50–59 and 60–69 years).

The calculation of χ^2 test for homogeneity of proportions was performed. For statistical analyses, software SPSS version 17 (SPSS, Chicago, IL) was used. A p value lower than 0.05 was considered as significant.

3. Results

Between 2001 and 2006, a total of 145 ICs were reported, ten of them (7%) being DCIS. The sensitivity of the program, i.e., the rate between the 476 screen detected breast cancers and overall breast cancers (screen detected ones plus 145 ICs) in the same period was 77% (476/621). During the first year, 32% (46/145) of ICs were reported (first semester, 9% [13/145]; second semester, 23% [33/145]), while they were 68% (99/145) during the second year (first semester, 33% [48/145]; second semester, 35% [51/145]). The absolute incidence of ICs from 2001 to 2006 was 17 per 10,000 screening examinations (Table 1, Fig. 1). Of all 145 ICs, 95% (138/145) were diagnosed after a negative first screening examination, and 5% (7/145) were diagnosed after a negative work-up.