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In situ breast cancer: Incidence trend and organised screening programmes in Italy

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Abstract

The effect of mammography screening programmes on the incidence of *in situ* breast cancer (CIS) is described by analysis of the CIS incidence trend in the 1990s and comparison of pre-screening and screening periods in six areas of Italy. All 1069 CIS arising in women aged 40–79 years between 1988 and 1999 were analysed through age-standardised rates and Poisson regression models. The results show that, for the whole series, ductal carcinoma *in situ* (DCIS) represented 89% and lobular carcinoma *in situ* (LCIS) 11% of CIS detected. For all six areas, the introduction of screening increased the incidence of DCIS (screening/pre-screening ratio, range 1.12–1.77). Overall, DCIS represented 11% (226/2022) of all screening-detected cancers. A significant increasing trend in DCIS incidence during the 1990s and a modification in pattern of age-specific incidence rates after the beginning of screening programmes were observed. This increase can largely be explained by screening programmes. The incidence observed during the screening period was a persistent 39% higher than during the pre-screening period, after adjustment for the ''percentage of cases diagnosed by screening''. The increase also involves women at an age not targeted by screening programmes. In conclusion, as the increasing trend in DCIS is not completely explained by the effect of the screening programmes, this supports the use of mammography as a ''spontaneous'' preventive practice during ongoing organised screening programmes, particularly among age groups not usually invited for

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screening. Therefore, the effect of mammography on stage-specific incidence of CIS may be more marked than expected on the basis of the effect of screening programmes.

Keywords: *In situ* breast cancer; Stage; Mammography screening; Incidence

1. Introduction

Since the early 1980s, the incidence of breast carcinoma *in situ* (CIS) has increased markedly in those areas of the United States of America (USA) included in the SEER program. This is due largely to an increase in incidence of ductal carcinoma *in situ* (DCIS). The widespread adoption of mammography screening has been considered largely responsible for the rise in incidence of DCIS [1]. Similar trends have been observed in other countries [2,3]. Currently in the USA, 12–15% of newly diagnosed breast cancer cases are DCIS, of which at least 90% are diagnosed by mammography [4]. In the UK, DCIS represents about 20% of screen-detected breast cancers [5].

DCIS represents a precursor of invasive breast cancer [6], but DCIS is a biologically and morphologically heterogeneous disease and the lesions vary in their propensity to recur or progress to invasive cancer [1,4,7]. In particular, the clinical significance of DCIS detectable by mammography alone is not well established, as it is uncertain whether its biological potential is the same as for clinically diagnosed DCIS [8]. The relevance of detection of DCIS in a screening programme therefore remains controversial, even if the high-quality mammography required to detect small invasive cancers will inevitably detect DCIS [9]. Recent studies suggest that overdiagnosis and overtreatment of DCIS in breast cancer screening is modest in absolute terms (37% of DCIS diagnosed at first screening and 4% at incidence screening are estimated to be non-progressive) compared with the likely benefit of early diagnosis and treatment of progressive lesions [9].

Since 1996, the Italian Ministry of Health has promoted local mammography screening programmes based on the use of nationally agreed protocol, offering two-view mammography to women aged 50–69 years (with and inter-screening interval of 2 years). The presence in the screening area of a population-based breast cancer registry is one of the conditions recommended for the quality control of screening. In this context, in the 1990s, some regional governments in Italy introduced mammography screening programmes based on personal invitation. The screening was introduced mainly in areas where a population-based cancer registry was already operating.

This paper describes the effect of breast cancer screening on the incidence of CIS in six areas of Italy (located in central and northern Italy) where a population-based cancer registry was operating and mammography screening was ongoing. The link between cancer registries and screening databases allowed the assessment of the circumstances of cancer diagnosis.

2. Materials and methods

2.1. Population under study and source of cases

The whole series collected in the SCREENREG study (Cancer Registries and Screening Programmes Monitoring) included 17,172 invasive and CISs (ICD-9 174 and 233.0) diagnosed between 1988 and 1999 in women aged 40–79 years who were residing in the six areas of Italy under study. The characteristics, structure and setting of the study, together with the results referring

Table 1
Italian registries participating in the study: period of incidence by screening period, women resident in the area (mean number/year) and *in situ* incident cases included in the study by screening period and registry (age range 40–79 years), percentage of screening-detected DCIS by registry (age range 50–69 years)

Cancer registry	Period		Women resident ($n \times 1000$)	Cases included in the study (n)		Screening-detected[c] DCIS (%)
	Pre-screening	Screening		Pre-screening	Screening	
Ferrara	1992–1997 (Oct.)	1997 (Nov.)–1999	99	67	33	70
Florence City	1988–1990 (Sept.)	1990 (Oct.)–1996	114	31	108	63
Modena[a]	1992–1995 (Sept.)	1995 (Oct.)–1998	153	93	173	41
Parma	1994 and 1997	1998	103	24	26	46
Romagna	1989–1994	1997–1999	188	84	216	60
Turin City[b]	1988–1991	1992–1995	254	68	146	41

[a] Program limited to some municipalities of the areas covered by the cancer registry.
[b] Programme inviting women aged 50–59 years.
[c] Based on cases detected during the screening period.

to invasive cases, have been detailed elsewhere [10]. The present analysis focused on CIS incidence trends.

More than 900,000 women were residing in the six areas (Table 1). Each registry contributed to this study by supplying data for a variable number of years, depending on the availability of incidence data and on the starting year of screening, for a total of about 7.5 million person-years. The population size included in the study was stable before and after the beginning of screening in all registries, except for Romagna where the population covered by cancer registration increased during the screening period (from 158,000 to 248,000 women). The year that screening started differed by area: being earlier in Florence and Turin, and later in Ferrara and Parma (where screening began in 1997–1998). Overall, 1069 CIS were recorded. Every registry checked the circumstances of diagnosis of each case through the screening programme databases. Cases were categorised as either "screen-detected" or "diagnosed at the current clinical practice". The latter group included cancers occurring in women who had not been invited to screening, in those who did not attend the screening and patients with interval cancer.

2.2. Analysis

Age-adjusted incidence rates (age range 40–79 years; standard: European population) by registry and by period of incidence were calculated. Furthermore, multiple Poisson regression models were fitted to assess the effect on incidence of the age-registry-specific percentage of breast cancers diagnosed at screening and of the diagnosis period (screening versus pre-screening) adjusted for 5-year age groups and registry. The percentage of breast cancers (*in situ* + invasive cases) diagnosed through screening represents a proxy variable indicating the impact of the programme in the area, depending on the proportion of women invited at a given time, on their compliance and on the sensitivity of the programme itself. The models were checked against the data using deviance, a measure of discrepancy between observed and fitted values. The statistical significance of the variables included in the model was assessed on the basis of the likelihood ratio statistic (LRS). Incidence rate ratios (IRR) and 95% confidence intervals (95% CI) were calculated. Analyses were carried out using the STATA statistical package (version 6.0, Stata Corporation, College Station, TX, USA, 1999).

3. Results

Among women in the age range 40–79 years, a total of 367 CIS were diagnosed in the pre-screening period and 704 in the screening period. DCIS represented 89% and lobular carcinoma *in situ* (LCIS) 11% of the whole series. Overall, DCIS represented 11% (226/2022) of all screening-detected cancers. The proportion ranged from 15% in the age range 50–54 years, to 11–12% in the age range 55–64 years, to 8% in the age range 65–69 years and to 11% in the age range 70–74 years. During the screening period, the percentage of DCIS diagnosed at screening in women aged 50–69 years was in the range 41–70% throughout the registries, due to some differences in the screening programmes. In fact, during the years studied, the screening did not involve all the municipalities in the area covered by the Modena Registry, while the invitation was addressed to women in the age range 50–59 years in Turin.

Table 2
Pre-screening incidence rates (age-adjusted, standard: European population, per 100,000) of ductal carcinoma *in situ* (DCIS) by cancer registry and screening period, and screening/pre-screening incidence rate ratio (IRR), age range 40–79 years

Registry	DCIS			
	Pre-screening period		Screening/pre-screening IRR	
	Incidence rate	95% CI		
Ferrara[a]	10.2	6.2–14.2	1.12	$P = 0.43$
Florence[a]	9.3	5.6–12.9	1.36	$P = 0.008$
Modena	13.9	10.8–17.1	1.51	$P < 0.001$
Parma	10.3	5.6–15.1	1.56	$P = 0.004$
Romagna[a]	8.6	6.1–11.0	1.77	$P < 0.001$
Turin	5.1	3.7–6.5	1.56	$P < 0.001$

[a] The years analysed in the pre-screening and in the screening periods were those reported in Table 1, with the exceptions of Florence (screening period: October 1990–1993), Ferrara (pre-screening period: 1995–October 1997) and Romagna (pre-screening period: 1992–1994).

Table 2 shows age-adjusted incidence rates of DCIS. For some registries, in which a long period of incidence was available, this was subdivided into 3-year periods, and for the analysis only the periods immediately before and after the start of screening were considered. During the pre-screening period, age-adjusted incidence rates ranged from 5.1 per 100,000 to 13.9 per 100,000. During the screening period, incidence rates were higher in all areas, the screening/pre-screening rate ratio ranging from 1.12 to 1.77.

A multivariate analysis of the pooled data-set was performed by comparing the periods of diagnosis immediately before and after the beginning of screening. A model including registry, age, percentage of all screen-detected cases (a proxy of screening impact) and period of diagnosis was fitted (deviance: $P = 0.10$). As expected, the effect of mammography screening largely explains the incidence trend in DCIS, an increase of 9% (95% CI: 2–15) for every 10% increase in all screen-detected cases. Nevertheless, the screening did not completely explain the increase in incidence rates. Indeed, after the beginning of screening, the multivariate model showed that DCIS incidence continued to be 39% higher (95% CI: 25–54) than during the pre-screening period.

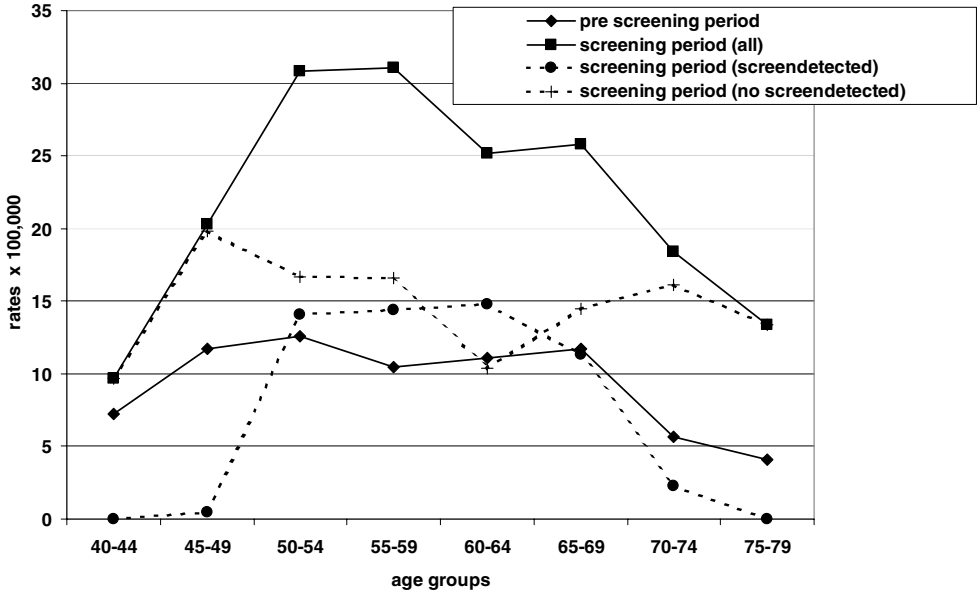

Fig. 1. *In situ* breast cancer (CIS): age-specific incidence rates by period and modality of diagnosis.

In the pooled data-set, before the beginning of the screening programmes, the age-specific CIS incidence rates (Fig. 1) were substantially stable until 69 years of age, then fell progressively. After screening began, the pattern of age-specific modified, increasing 2–3 times between 50 and 69 years of age. The screening-detected cases largely explained this rise, even if, in women aged 50–69 years, the incidence rates of cases diagnosed outside screening were moderately higher than the corresponding rates during the pre-screening period. The incidence rise was also observed in women aged 40–49 years and 70–79 years (about 1.5 and 3 times, respectively) who were not involved in the screening programmes. The analysis stratified by morphology showed that the increase substantially concerned DCIS, whereas LCIS incidence rates were only marginally modified (data not shown).

The analysis of DCIS incidence of the pooled data-set by calendar period (reference: 1988–1990; Fig. 2) showed, for those aged 50–69 years, a significantly

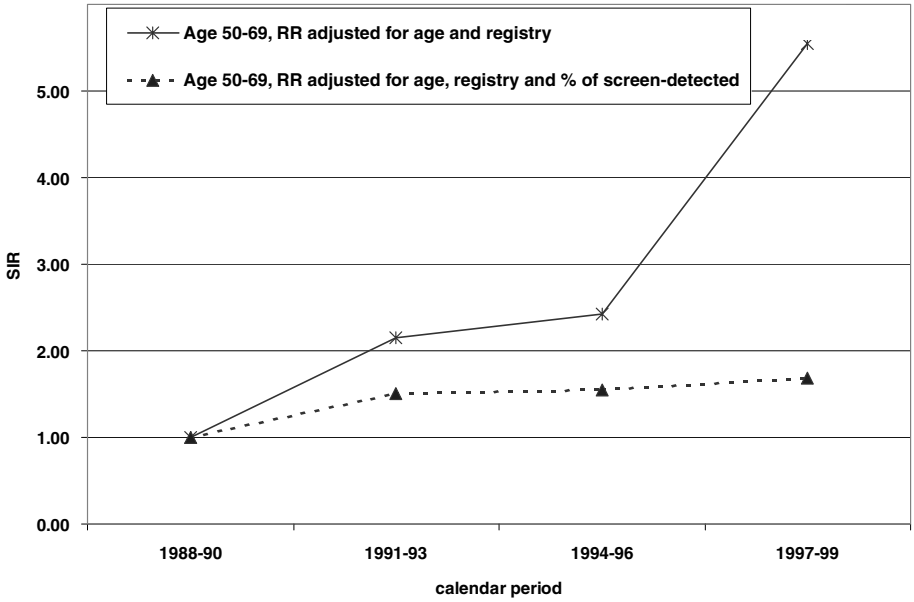

Fig. 2. Time trend in incidence of ductal carcinoma *in situ* (DCIS) of the breast.

increasing trend ($P < 0.001$) when the effect of diagnosis calendar-year was adjusted for age and registry. When the model also included the percentage of screening-detected cases, the curves flattened but the differences generally continued to be significant (1991–1993: IRR, 1.51; 95% CI, 1.04–2.20; 1994–1996: IRR, 1.55; 95% CI, 1.02–2.37; 1997–1999: IRR, 1.68; 95% CI, 0.82–3.46). Also women aged 40–49 years and 70–79 years showed an increasing trend per calendar period. Nevertheless, pooled models had an insufficient fit (model deviance: $P = 0.025$ and $P = 0.011$, respectively), suggesting non-homogeneous age-specific patterns among the registries.

4. Discussion

The effect of mammography screening programs on CIS incidence rates is shown in six areas of Italy for women aged 40–79 years. As the programmes targeted women in the age range 50–69 years, the study also included age groups not involved in the screening. The analysis of a wide age range allows the assessment of a more complete picture of the effect, from a population-based perspective, of diagnostic modifications concomitant with the beginning of screening. The cases, identified by qualified population-based cancer registries [11], can be considered fully representative of all those occurring in the resident population.

The study showed a significantly increasing trend in DCIS incidence during the 1990s, which is largely, but not completely, explained by the screening, and a modification of pattern of age-specific incidence rates after the beginning of screening programmes. This screening effect was expected and consistent with findings from previous studies, and showed a marked increase in DCIS due to the increased use of mammography [1,2,5]. Nevertheless, in our area, the rise in incidence of DCIS is not completely explained by the screening. Indeed, the incidence in the screening period continued to be 39% higher than in the pre-screening period after the adjustment for the ''percentage of cases diagnosed at screening''. This variable is a proxy of the impact of the programme in the target population, representing both the proportion of women invited and their compliance, and of the sensitivity of the programme itself. Also the analysis of the age-specific incidence showed that, after the introduction of screening, the rates of DCIS diagnosed outside screening were higher than the corresponding rates in the pre-screening period. This increase concerned women in the age groups not invited to screening and, marginally, in those targeted in the screening programmes.

Aside from screening, other factors were taken into account as possible causes of the increasing trend in breast cancer incidence, including changes in clinical examination or breast self-examination and cohort or period effects of risk factors, such as the use of hormone replacement therapy, change in reproductive patterns and obesity in postmenopausal women [12–14].

A previous analysis, carried out in the same areas and periods, showed that the increasing incidence of invasive breast cancer observed after screening started was substantially explained by the increase in detection of ''early-stage'' cancer, as a consequence of the screening itself, rather than by a ''real'' increase in the background incidence [10].

As far as CIS is concerned, the increasing incidence trend observed in the SEER areas (USA) persisted until the late 1990s [15]. In the UK, the rate of CIS detected in women becoming newly eligible for screening (first test following first invitation) is higher than the quality target suggests [5]. Our study, which is mostly limited to the first few years after screening began, does not allow us to evaluate more closely the secular trend in DCIS and, therefore, further periods of incidence need to be analysed.

A failure in the linkage between cancer registry and screening databases, and the consequent incorrect classification of some cases as ''unscreened'', could represent a possible limitation of this study. In our opinion, errors in correctly ascertaining the circumstances of diagnosis did not seriously affect the results. Indeed, the increase in CIS diagnosed in unscreened women mainly concerns ages that are not involved in screening. Furthermore, the six cancer registries were involved in the quality control of the screening programmes and the circumstances of diagnosis of cases in the screening ages were carefully checked.

As reported in other countries, increased debate and publicity about breast cancer screening during the introduction of screening programmes can bring about an improvement in public awareness, resulting in the earlier detection of tumours [16]. Widespread use of mammography as a preventive practice outside screening programmes has been documented in several populations [17–20]. An increase in the detection of small invasive cancer in unscreened women as an effect of this practice has also been reported [21]. Our data also confirm these results for CIS and show that the widespread use of mammography as a ''spontaneous'' preventive practice can coexist with an ongoing, organised screening programme, especially among age groups not involved in the programmes. Therefore, at a population level, the effect of mammography on stage-specific incidence rates may be larger than expected on the basis of the compliance with screening programmes.

From a general point of view, undesirable side-effects can affect the use of mammography as a ''spontaneous'' preventive practice (i.e., lower sensitivity in younger patients) and this can indirectly decrease the cost-effectiveness of screening programmes. On the other hand,

chronological age alone should not be considered a reason for the cessation of screening in older women who are in reasonably good health (i.e., over 70 years of age) [22].

In conclusion, this study showed an increasing trend in DCIS, which can largely, but not completely, be explained by the effect of the screening programs. The results support the use of mammography as a "spontaneous" preventive practice concomitant with organised, ongoing screening programmes. The effects of mammography on the stage-specific incidence trend may, therefore, be larger than expected on the basis of the screening programme effect.

Conflict of interest statement

None declared.

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